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[Intervention Review]

Transperitoneal versus retroperitoneal laparoscopic adrenalectomy for adrenal tumours in adults

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ABSTRACT

Background

Laparoscopic adrenalectomy is an accepted treatment worldwide for adrenal gland disease in adults. The transperitoneal approach is more common. The retroperitoneal approach may be preferred, to avoid entering the peritoneum, but no clear advantage has been demonstrated so far.

Objectives

To assess the effects of laparoscopic transperitoneal adrenalectomy (LTPA) versus laparoscopic retroperitoneal adrenalectomy (LRPA) for adrenal tumours in adults.

Search methods

We searched CENTRAL, MEDLINE, Embase, ICTRP Search Portal, and ClinicalTrials.gov to 3 April 2018. We applied no language restrictions.

Selection criteria

Two review authors independently scanned the abstract, title, or both sections of every record retrieved to identify randomised controlled trials (RCTs) on laparoscopic adrenalectomy for preoperatively assessed adrenal tumours. Participants were affected by corticoid and medullary, benign and malignant, functional and silent tumours or masses of the adrenal gland, which were assessed by both laboratory and imaging studies.

Data collection and analysis

Two review authors independently extracted data, assessed trials for risk of bias, and evaluated overall study quality using GRADE criteria. We calculated the risk ratio (RR) for dichotomous outcomes, or the mean difference (MD) for continuous variables, and corresponding 95% confidence interval (CI). We primarily used a random-effects model for pooling data.

Main results

We examined 1069 publications, scrutinized 42 full-text publications or records, and included five RCTs. Altogether, 244 participants entered the five trials; 127 participants were randomised to retroperitoneal adrenalectomy and 117 participants to transperitoneal adrenalectomy. Two trials had a follow-up of nine months, and three trials a follow-up of 31 to 70 months. Most participants were women, and the average age was around 40 years. Three trials reported all-cause mortality; in two trials, there were no deaths, and in one trial with six years of follow-up, four participants died in the LRPA group and one participant in the LTPA group (164 participants; low-certainty evidence). The trials did not report all-cause morbidity. Therefore, we analysed early and late morbidity, and included specific adverse events under these outcome measures. The results were inconclusive between LRPA and LTPA for early morbidity (usually reported within 30 to 60 days after surgery; RR 0.56, 95% CI 0.27 to 1.16; $P = 0.12$; 5 trials, 244 participants; very low-certainty evidence). Nine out of 127 participants (7.1%) in the LRPA group, compared with 16 out of 117 participants (13.7%) in the LTPA group experienced an adverse event. Participants in the LRPA group may have a lower risk of developing late morbidity (reported as latest available follow-up; RR 0.12, 95% CI 0.01 to 0.92; $P = 0.04$; 3 trials, 146 participants; very low-quality evidence). None of the 78 participants in the LRPA group, compared with 7 of the 68 participants (10.3%) in the LTPA group experienced an adverse event.

None of the trials reported health-related quality of life. The results were inconclusive for socioeconomic effects, assessed as time to return to normal activities and length of hospital stay, between the intervention and comparator groups (very low-certainty evidence). Participants who had LRPA may have had an earlier start on oral fluid or food intake (MD -8.6 hr, 95% CI -13.5 to -3.7; $P = 0.0006$; 2 trials, 89 participants), and ambulation (MD -5.4 hr, 95% CI -6.8 to -4.0 hr; $P < 0.0001$; 2 trials, 89 participants) than those in the LTPA groups. Postoperative and operative parameters (duration of surgery, operative blood loss, conversion to open surgery) showed inconclusive results between the intervention and comparator groups.

Authors' conclusions

The body of evidence on laparoscopic retroperitoneal adrenalectomy compared with laparoscopic transperitoneal adrenalectomy is limited. Late morbidity might be reduced following laparoscopic retroperitoneal adrenalectomy, but we are uncertain about this effect because of very low-quality evidence. The effects on other key outcomes, such as all-cause mortality, early morbidity, socioeconomic effects, and operative and postoperative parameters are uncertain. LRPA might show a shorter time to oral fluid or food intake and time to ambulation, but we are uncertain whether this finding can be replicated. New long-term RCTs investigating additional data, such as health-related quality of life, surgeons' level of experience, treatment volume of surgical centres, and details on techniques used are needed.

PLAIN LANGUAGE SUMMARY

Transperitoneal versus retroperitoneal laparoscopic adrenalectomy for adrenal tumours in adults

Review question

What are the effects of laparoscopic retroperitoneal adrenalectomy compared with laparoscopic transperitoneal adrenalectomy in adults?

Background

The adrenal glands are found above the kidneys, and produce several hormones, such as adrenaline, aldosterone, and cortisol. A tumour of the adrenal gland may be benign or cancerous, and is often found during routine examinations, such as ultrasonography of the belly (abdomen). The surgical removal of one or both adrenal glands (adrenalectomy) is usually recommended if the adrenal mass is more than 4 cm in diameter, if the mass enlarges by 1 cm or more during the period of observation, or if evidence of autonomous hormonal secretion develops.

There are several techniques to remove an adrenal gland. Nowadays, surgeons most often use keyhole surgery (laparoscopic surgery) instead of open surgery, using small cuts in the belly to introduce special surgical instruments and a small camera (laparoscope) with light. Laparoscopic transperitoneal adrenalectomy uses a cut through the belly that includes cutting a special membrane inside the belly (peritoneum) to expose the adrenal gland. Laparoscopic retroperitoneal adrenalectomy approaches the adrenal gland from the back, without cutting the peritoneum. Advocates of the latter technique have proposed better results, like shorter operative time, less blood loss, less postoperative pain, and shorter hospital stay.

Study characteristics

We found five randomised controlled trials (clinical trials where people are randomly put into one of two or more treatment groups) with 244 participants. A total of 127 participants were randomised to retroperitoneal adrenalectomy and 117 participants to transperitoneal adrenalectomy. Two studies had an observation period after surgery of nine months. Three studies observed their participants for 31 to 70 months. Most participants were women, and the average age was around 40 years.

This evidence is up to date as of April 2018.

Key results

In the short-term period after surgery, no deaths were reported for either adrenalectomy technique. One study with a six-year observation period, reported that out of 164 participants, four participants from the retroperitoneal adrenalectomy group died, and one participant from the transperitoneal adrenalectomy group died. We compared early poor health (morbidity), reported after 30 to 60 days, and late morbidity, reported at the longest observation time after surgery. Early morbidity was comparable between the two techniques, but late morbidity might be lower following retroperitoneal adrenalectomy (none out of 78 participants) than following transperitoneal adrenalectomy (7 out of 68 participants). No study reported on health-related quality of life. Time to return to normal activities, length of hospital stay, duration of surgery, operative blood loss, and a change to open surgery were comparable between the two techniques. Time to oral fluid or food intake and time getting out of bed and engaging in light activity seemed a couple of hours shorter following retroperitoneal adrenalectomy (on average 8.6 hours) compared to transperitoneal adrenalectomy (on average 5.4 hours).

Certainty of the evidence

We are uncertain which adrenalectomy technique is best, mainly because of the small number of studies, small number of participants, and some systematic errors in the majority of our analysed studies. New studies should especially investigate health-related quality of life. Surgeons' level of experience and treatment volume of surgical centres might also influence results.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Laparoscopic retroperitoneal adrenalectomy compared to laparoscopic transperitoneal adrenalectomy for adrenal tumours in adults

Laparoscopic retroperitoneal adrenalectomy compared to laparoscopic transperitoneal adrenalectomy for adrenal tumours in adults

Patient: adults with adrenal tumours

Settings: inpatients

Intervention: laparoscopic retroperitoneal adrenalectomy (LRPA)

Comparison: laparoscopic transperitoneal adrenalectomy (LTPA)

Outcomes	Assumed risk	Corresponding risk	Relative effect (95% CI)	No of participants (trials)	Certainty of the evidence (GRADE)	Comments
	LTPA	LRPA				
All-cause mortality Follow-up: median 31 months	See comment			164 (3)	⊕⊕⊕⊕ low ^a	3 trials reported on mortality: 2 reported no deaths; in 1 trial, 4 participants died in the LRPA group and 1 participant in the LTPA group (6-year follow-up)
Early morbidity (any complication during the first 30 to 60 days following surgery) Follow-up: 60 days	137 per 1000	77 per 1000 (37 to 159)	RR 0.56 (0.27 to 1.16)	244 (5)	⊕⊕⊕⊕ very low ^b	-
Late morbidity (any complication following surgery at latest available follow-up) Follow-up: median 31 months	103 per 1000	12 per 1000 (1 to 95)	RR 0.12 (0.01 to 0.92)	146 (3)	⊕⊕⊕⊕ very low ^b	-

Health-related quality of life	Not reported					
Socioeconomic effects						
a. Time to return to normal activities	a. The mean number of days to return to normal activities across control groups (range 12.5 days to 32.9 days)	a. The mean number of days to return to normal activities in the LRPA groups were 1.3 days shorter (5.4 days shorter to 2.8 days longer)	-	a. 102 (3) b. 89 (2) c. 250 (5)	a, b, and c ⊕⊕⊕⊕ very low ^c	a. normal activities had unclear definitions
b. Time to ambulation						
c. Length of hospital stay	b. The mean number of hours to ambulation across control groups (range 11.5 hr to 40.8 hr)	b. The mean number of hours to ambulation in the LRPA groups were 5.4 hr shorter (6.8 hr shorter to 4.0 hr shorter)				
Follow-up: median 31 months	c. The mean number of days of hospital stay across control groups (range 1.0 day to 6.0 days)	c. The mean number of days of hospital stay in the LRPA groups were 0.4 days shorter (1.2 days shorter to 0.4 days longer)				

*The basis for the **assumed risk** (e.g. the mean control group risk across trials) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the control group and the **relative effect** of LRPA (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **hr:** hour(s)

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

*Assumed risk was derived from the event rates in the comparator groups

^aDowngraded by two levels because of serious imprecision (low number of participants and trials) - see [Appendix 15](#)

^bDowngraded by three levels because of high risk of performance and detection bias and serious imprecision - see [Appendix 15](#)

^cDowngraded by one level because of unclear risk of performance and detection bias, and by two levels because of (serious) imprecision (low to moderate number of participants and trials) - see [Appendix 15](#)

BACKGROUND

Description of the condition

Tumours or masses of the adrenal gland are quite common and usually unilateral. They may originate from the adrenal corticoid or the adrenal medulla of the gland. They are categorised as either functional (hormone-secreting) or silent (non hormone-secreting). Moreover, as any tumoral tissue, they may be benign or malignant. The majority of adrenocortical tumours are benign, non-functioning adenomas, which are discovered incidentally on abdominal imaging studies. This is usually called an adrenal 'incidentaloma'. Hormone-secreting adrenocortical tumours are generally discovered because their symptoms cause Cushing's syndrome (showing enhanced secretion of adrenocorticotrophic hormone, primary aldosteronism, or much less commonly, virilization). Carcinomas of the adrenal corticoid are quite rare, but can be aggressive. More rarely, tumours arise from the medulla of the gland. These are called pheochromocytomas. Pheochromocytomas are catecholamine-secreting tumours that arise from chromaffin cells of the adrenal medulla. They may be benign or malignant.

Description of the intervention

Adrenalectomy is usually recommended if the adrenal mass is 4 cm or larger in diameter, if the mass enlarges by 1 cm or more during the period of observation, or if evidence of autonomous hormonal secretion develops (Young 2007). Open transperitoneal adrenalectomy was the gold standard of treatment for adrenal disease until 1992, when laparoscopic adrenalectomy was first described as a transperitoneal technique (Gagner 1992).

Laparoscopic transperitoneal adrenalectomy (LTPA) is performed under general anaesthesia; the individual is placed in lateral decubitus position, with the affected side elevated around 60°, usually with the help of a bean bag. The ipsilateral arm is generally supported by a metal L-shaped support that is secured to the table. Three to five transperitoneal ports are positioned through the anterior abdominal wall. After the adrenal gland space is exposed, the retroperitoneum is incised, and the gland dissected. On the left side, the descending colon is reflected medially; the adrenal vein is divided with bipolar diathermy or cutting between clips, and dissection is carried out, starting just superior to the renal vein, until the adrenal gland is freed. On the right side, the liver must be retracted, but the colon rarely requires mobilisation. The peritoneum is incised along the lateral aspect of the inferior vena cava, down to the superior edge of the renal vein. The short right adrenal vein is identified, and divided between clips. When the dissection of the gland is completed at the lateral side, the specimen is bagged and removed.

Laparoscopic retroperitoneal adrenalectomy (LRPA) was introduced in 1995 (Mercan 1995). In this technique, the surgeon approaches the adrenal gland directly through the retroperitoneal space, without breaching the peritoneum. Individuals are placed in the lateral decubitus position, and the table is flexed in order to expand the operating space between the 12th rib and the iliac crest. To obtain retroperitoneal access, a 1 cm skin incision is made below the 12th rib, and a space is created below the fascia by careful finger dissection. On the left side, the Gerota's fascia is incised around the superior aspect of the kidney, and dissection is continued medially along the renal vein, until the main adrenal vein is encountered and

divided between clips, until mobilisation is completed. On the right side, the investing fascial layer is opened transversely along the upper renal pole until the inferior vena cava is identified; dissection continues superiorly along its lateral edge to the right adrenal vein, which is divided between clips, completing mobilisation of the gland.

Adverse effects of the intervention

Intraoperative bleeding may occur in 1% to 4% of cases, depending on the techniques used (Constantinides 2012). Small liver injuries can occur during retraction or adrenal dissection on the right, which might be controlled by bipolar coagulation, simple compression, or placement of fibrin material to achieve haemostasis. Rarely, the surgeon may have to convert to open surgery. Vascular injuries, especially to the inferior vena cava, comprise almost 7% of all complications, and are the leading cause for conversion (Corcione 2001). Small injuries may be compressed and treated with coagulant agents; increasing the intra-abdominal pressure helps to control bleeding. If bleeding continues, laparoscopic suturing is an option, but only if the surgeon has sufficient experience and skills; otherwise, the surgeon should convert to open surgery. Inadvertent injuries of the diaphragm causing pneumothorax may occur occasionally, requiring direct diaphragm suture closure (Naito 1995). A chest tube placement is rarely required initially, although it may be required later if a significant pneumothorax develops. Injury to the spleen and the left side of the pancreas have also been reported (Greco 2011; Terachi 2000).

How the intervention might work

Numerous trials have shown the safety and feasibility of laparoscopy since its introduction in 1992. Several benefits were seen compared to open procedures: a decreased hospital stay, faster recovery, decreased pain and narcotic use, and fewer complications (Assalia 2004). Minimally invasive adrenalectomy is now considered the standard treatment for benign adrenal masses (Jacobs 1997). Laparoscopic retroperitoneal adrenalectomy was first performed and described in 1995 (Mercan 1995). By directly entering the retroperitoneal space, and not breaching the peritoneum, this technique showed the potential to result in a shorter operative time, less blood loss, less postoperative pain, and shorter hospital stay (Constantinides 2012). Despite reports of favourable results for minimally invasive adrenalectomy techniques, using either the transperitoneal or retroperitoneal route, only a few trials have compared the two techniques. They showed no superiority of either technique. However, most trials have been limited by a small sample size and a single-institution design.

Why it is important to do this review

The intrinsic difficulties of laparoscopic transperitoneal adrenalectomy limited the diffusion of the technique, which was performed in less than 20% of cases until 2006 (Murphy 2010). In the following years, demonstration of the general advantages of laparoscopy, such as reduced blood loss, shorter hospital stay, and faster return to normal activity, together with accumulated experience, reversed the trend in favour of a laparoscopic technique (Guazzoni 1995). Today, laparoscopic transperitoneal adrenalectomy has become the most widely used procedure for people with benign adrenal disease.

Introduced in 1995, laparoscopic retroperitoneal adrenalectomy was proposed as a good alternative in selected cases, and surgeons started to use it more frequently (Mercan 1995). Potential advantages were the same; shorter operative time, less postoperative pain, and shorter hospital stay (Constantinides 2012). Some trials have compared the outcomes of laparoscopic transperitoneal adrenalectomy and laparoscopic retroperitoneal adrenalectomy, but their results are inconclusive because of their design and inclusion criteria. Several meta-analyses have compared laparoscopic transperitoneal and retroperitoneal adrenalectomy (Chen 2013; Constantinides 2012; Nigri 2013). However, these analyses were not fully reliable, because they included a small number of both observational and interventional trials, and heterogeneous trial populations. Recent randomised trials were not included, as they were published prior to the literature searches (Barczynski 2014; Mohammadi-Fallah 2013). Finally, the review authors did not adequately assess the risk of bias. Therefore, our systematic review will try to establish a reliable body of evidence of relevant outcomes in people undergoing either laparoscopic transperitoneal adrenalectomy or laparoscopic retroperitoneal adrenalectomy.

OBJECTIVES

To assess the effects of laparoscopic transperitoneal adrenalectomy versus laparoscopic retroperitoneal adrenalectomy for adrenal tumours in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled clinical trials (RCTs).

Types of participants

We included data from adults (older than 16 years) who underwent laparoscopic transperitoneal or laparoscopic retroperitoneal adrenalectomy for preoperatively assessed adrenal tumours.

Diagnostic criteria

Corticoid and medullary, benign and malignant, functional and silent tumours, or masses of the adrenal gland were assessed by both laboratory and imaging studies.

Types of interventions

We planned to investigate the following comparisons of intervention versus control/comparator.

Intervention

- Laparoscopic retroperitoneal adrenalectomy (LRPA), defined as any technique approaching the adrenal gland directly through the retroperitoneal space, and not breaching the peritoneum.

Comparator

- Laparoscopic transperitoneal adrenalectomy (LTPA), defined as any technique approaching the adrenal gland directly through the abdominal wall and peritoneal sac.

Concomitant interventions had to be the same in the intervention and comparator groups to establish fair comparisons.

Types of outcome measures

Primary outcomes

- All-cause mortality
- Early and late morbidity

Secondary outcomes

- Operative parameters
 - Duration of surgery
 - Intraoperative bleeding
 - Operative blood loss
 - Conversion to open surgery
- Postoperative parameters
 - Time to oral fluid or food intake
 - Chest infection or pleural effusion
 - Abdominal abscess
- Health-related quality of life
- Socioeconomic effects

Method of outcome measurement

- All-cause mortality: defined as death from any cause.
- Early and late morbidity: defined as any deviation from the regular postoperative course (e.g. chest infection, liver injury, splenic injury, vascular injury, pneumothorax or haemothorax, massive subcutaneous emphysema, surgical access site herniation).
- Duration of surgery: defined as the duration of general anaesthesia.
- Intraoperative bleeding: defined as the occurrence of blood loss greater than 200 mL.
- Operative blood loss: defined as the quantity of blood loss in millilitres (mL).
- Conversion to open surgery: defined as any technical failure requiring a larger skin incision before the complete dissection of the gland.
- Time to oral fluid or food intake: defined as the time to oral intake of fluids or food.
- Chest infection or pleural effusion: defined as any diagnosis of infection that affected the lungs (either larger or smaller air sacs), or the accumulation of fluid in the pleural space.
- Abdominal abscess: defined as "a pus-containing confined structure or collection, localised in abdominal cavity" (Schein 2010).
- Health-related quality of life: evaluated by a validated instrument such as the 36-item Short-Form Health Survey (SF-36).
- Socioeconomic effects: such as length of hospital stay, time to return to normal activities, time to ambulation (time to autonomous walking), and time to return to work.

Timing of outcome measurement

- All-cause mortality, early and late morbidity, socioeconomic effects: measured within 30 to 60 days after surgery and overall, during the entire follow-up provided.
- Duration of surgery: measured at the end of general anaesthesia.

- Operative blood loss, intraoperative bleeding, conversion to open surgery, splenic or liver injury, vascular injury: measured at the end of surgery.
- Time to oral fluid or food intake: measured within one week after surgery.
- Socioeconomic effects, pneumothorax or haemothorax, chest infection, pleural effusion: measured within 30 to 60 days after surgery.
- Health-related quality of life: measured within the first week, at 30 days after surgery, and overall, during the entire follow-up provided.

Search methods for identification of studies

Electronic searches

We searched the following sources from inception of each database to the specified date; we placed no restrictions on the language of publication.

- Cochrane Central Register of Controlled Trials (CENTRAL) via Cochrane Register of Studies Online (searched 3 April 2018).
- MEDLINE Ovid Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily, and MEDLINE (1946 to 3 April 2018).
- Embase Ovid (1974 to 2015 Week 13). RCTs indexed in Embase are now prospectively added to CENTRAL via a highly sensitive screening process ([CENTRAL creation details](#)).
- [ClinicalTrials.gov](#) (searched 3 April 2018).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch/; searched 3 April 2018).

For details on search strategies, see [Appendix 1](#). After submitting the review for editorial approval, the Cochrane Metabolic and Endocrine Disorders (CMED) Group's Information Specialist updated the literature search and send the results to the review authors. Had we identified new trials for inclusion, we would have evaluated them, incorporated the findings into our review, and resubmitted the updated review ([Beller 2013](#)).

Searching other resources

We tried to identify other potentially eligible trials or ancillary publications by searching the reference lists of included trials, (systematic) reviews, meta-analyses, and health technology assessment reports. In addition, we contacted authors of included trials in an attempt to identify trials we may have missed.

Data collection and analysis

Selection of studies

Two review authors (AA, RC) independently scanned the abstract, title, or both, of every record retrieved, to determine which trials should be assessed further. We investigated all potentially relevant articles as full text. We resolved any discrepancies through consensus, or by consulting with a third review author (GC). When we could not resolve a disagreement, we added the trial as a 'study awaiting classification', and contacted the trial authors for clarification. We present an adapted PRISMA flow diagram showing the process of trial selection ([Liberati 2009](#)).

Data extraction and management

For the trials that fulfilled our inclusion criteria, two review authors (AA, RC) independently extracted key participant and intervention characteristics. We reported data on efficacy outcomes and adverse events using standard data extraction templates as supplied by the CMED Group. We resolved any disagreements by discussion, or if required, by consulting a third review author (RP). For details see [Table 1](#); [Appendix 2](#); [Appendix 3](#); [Appendix 4](#); [Appendix 5](#); [Appendix 6](#); [Appendix 7](#); [Appendix 8](#); [Appendix 9](#); [Appendix 10](#); [Appendix 11](#); [Appendix 12](#); [Appendix 13](#); [Appendix 14](#); [Appendix 15](#).

We provided information, including the trial identification number, about potentially relevant ongoing trials in the Characteristics of ongoing studies table, and in the Matrix of trial endpoints (publications and trial documents), in [Appendix 7](#). We tried to find the protocol for each included trial. If successful, we reported primary, secondary, and other outcomes, and compared them with the data provided in publications, in [Appendix 7](#).

We sent an email request to all authors of included trials to enquire whether they were willing to answer questions regarding their trials. [Appendix 14](#) shows the results of this survey. Thereafter, we sought relevant missing information on the trial from them, if required.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary trial, we maximised our yield of information by collating all available data, and using the most complete dataset, aggregated across all known publications.

Assessment of risk of bias in included studies

Two review authors (AA, RC) independently assessed the risk of bias of each included trial. We resolved any disagreements by consensus, or by consultation with a third review author (GC).

We used the Cochrane 'Risk of bias' assessment tool, and assigned assessments of low, high, or unclear risk of bias ([Higgins 2017](#); [Appendix 2](#); [Appendix 3](#)). We evaluated individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions*, according to the criteria and associated categorisations contained therein ([Higgins 2017](#)).

Summary assessment of risk of bias

We presented a 'Risk of bias' graph and a 'Risk of bias' summary figure.

We distinguished between self-reported, investigator-assessed, and adjudicated outcome measures.

We defined the following endpoints as self-reported outcomes.

- Health-related quality of life

We defined the following endpoints as investigator-assessed outcomes.

- All-cause mortality
- Early and late morbidity
- Operative and postoperative parameters
- Socioeconomic effects

Risk of bias for a trial across outcomes

Some risk of bias domains, such as selection bias (sequence generation and allocation sequence concealment), affect the risk of bias across all outcome measures in a trial. In cases of high risk of selection bias, we marked all endpoints investigated in the associated trial as being at high risk. Otherwise, we did not perform a summary assessment of the risk of bias across all outcomes for a trial.

Risk of bias for an outcome within a trial and across domains

We assessed the risk of bias for an outcome measure by including all entries relevant to that outcome (i.e. both trial-level entries and outcome-specific entries). We considered low risk of bias to denote a low risk of bias for all domains, unclear risk to denote an unclear risk of bias for one or more domains, and high risk to denote a high risk of bias for one or more domains.

Risk of bias for an outcome across trials and across domains

These are the main summary assessments that we incorporated into our judgments about the quality of evidence in the 'Summary of findings' tables. We defined outcomes as at low risk of bias when most information came from trials at low risk of bias, unclear risk when most information came from trials at low or unclear risk of bias, and high risk when a sufficient proportion of information came from trials at high risk of bias.

Measures of treatment effect

When at least two trials were available for a comparison and a given outcome, we expressed dichotomous data as risk ratios (RRs) or risk differences (RD) with 95% confidence intervals (CIs). We expressed continuous data as mean differences (MDs) or standardised mean differences (SMDs) with 95% CIs. We expressed time-to-event data as hazard ratios (HRs) with 95% CIs.

Unit of analysis issues

We had planned to take into account the level at which randomisation occurred, such as cross-over trials, cluster-randomised trials, and multiple observations for the same outcome.

Dealing with missing data

If possible, we obtained missing data from trial authors, and carefully evaluated important numerical data, such as screened and randomised participants, as well as intention-to-treat (ITT), as-treated and per-protocol populations. We investigated attrition rates (e.g. drop-outs, losses to follow-up, withdrawals), and we critically appraised issues of missing data and imputation methods (e.g. last observation carried forward).

Where means and standard deviations (SDs) for outcomes were not reported, and we had not received the needed information from trial authors, we imputed these values by estimating the mean and variance from the median, range, and the size of the sample (Hozo 2005), or by assuming the standard deviation of the missing outcome to be the average of the standard deviations from trials where this information was reported.

We had planned to investigate the impact of imputation on meta-analyses, by means of sensitivity analysis.

Assessment of heterogeneity

In the event of substantial clinical, methodological, or statistical heterogeneity, we did not report trial results as the pooled effect estimate in a meta-analysis.

We identified heterogeneity (inconsistency) through visual inspection of the forest plots, and by using a standard χ^2 test with a significance level of $\alpha = 0.1$ (Deeks 2017). In view of the low power of this test, we also considered the I^2 statistic, which quantifies inconsistency across trials to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003).

Had we found heterogeneity, we would have attempted to determine possible reasons for it, by examining individual trial and subgroup characteristics.

Assessment of reporting biases

Because there were fewer than 10 trials investigating any outcome, we did not construct a funnel plot to assess small-study effects. Therefore, we interpreted results carefully (Sterne 2011).

Data synthesis

Even if there was good evidence for homogeneous effects across trials, we summarised primarily low risk of bias data using a random-effects model because such models are more appropriate in medical decision-making contexts, especially when there are rare events (Ades 2005; DerSimonian 1986; Fleiss 1991; Shuster 2007). We interpreted random-effects meta-analyses with consideration of the whole distribution of effects, ideally by presenting a prediction interval (Higgins 2009). A prediction interval specifies a predicted range for the true treatment effect in an individual trial (Riley 2011). We performed statistical analyses according to the statistical guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017).

Subgroup analysis and investigation of heterogeneity

We expected the following characteristics to introduce clinical heterogeneity, and had intended to carry out subgroup analyses to investigate the interactions (Altman 2003).

- Tumour size: < 6 cm versus ≥ 6 cm.
- Previous abdominal surgery: yes or no.
- Body mass index (BMI): < 30 kg/m² versus ≥ 30 kg/m².

However, there were not enough data to carry out these analyses.

Sensitivity analysis

We had intended to perform sensitivity analyses to explore the influence of the following factors (when applicable) on effect sizes, by restricting analysis to the following.

- Published trials.
- Effect of risk of bias, as specified in the [Assessment of risk of bias in included studies](#) section.
- Very long or large trials, to establish the extent to which they dominate the results.
- Using the following filters: diagnostic criteria, imputation, language of publication, source of funding (industry versus other), or country.

However, there were too few trials to carry out these analyses.

We tested the robustness of the results by repeating the analysis using different measures of effect size (RR, OR, etc.), and different statistical models (fixed-effect and random-effects models).

Certainty of the evidence

We assessed the overall quality of the evidence for each outcome specified below, according to the GRADE approach, which takes into account issues related to both internal validity (risk of bias, inconsistency, imprecision, publication bias) and external validity, such as directness of results. Two review authors (AA, RC) independently rated the quality for each outcome. We resolved any differences in assessment by discussion, or consulting a third review author (NN).

We also established an appendix entitled 'Checklist to aid consistency and reproducibility of GRADE assessments' to help with standardisation of our 'Summary of findings' table results ([Meader 2014](#)). Alternatively, we planned to use GRADEpro GDT software, and present evidence profile tables as an appendix ([GRADEpro GDT 2015](#)). We presented results for the outcomes as described in the [Types of outcome measures](#) section. If we were unable to complete a meta-analysis, we presented the results in a narrative format in the 'Summary of findings' table. We justified all decisions to downgrade the quality of the evidence using footnotes, and made comments to aid the reader's understanding of the Cochrane Review, where necessary.

Summary of findings table

We presented a summary of the evidence in a 'Summary of findings' table. This provided key information about the best estimate of the magnitude of the effect, in relative terms and as absolute differences, for each relevant comparison of alternative

management strategies. It also includes the number of participants and trials addressing each important outcome, and a rating of overall confidence in effect estimates for each outcome. We created the 'Summary of findings' table based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Schünemann 2017](#)), using Review Manager 5 table editor ([RevMan 2014](#)). We reported the following outcomes, listed according to priority.

1. All-cause mortality
2. Early morbidity
3. Late morbidity
4. Health-related quality of life
5. Socioeconomic effects

RESULTS

Description of studies

For a detailed description of trials, see the '[Characteristics of included studies](#)', '[Characteristics of excluded studies](#)' and '[Characteristics of ongoing studies](#)' sections.

Results of the search

Our comprehensive literature searches identified a total of 1229 records. There were 1069 records after removing duplicates. From these, we identified 42 full-text articles and records for further examination. We excluded the other publications on the basis of titles or abstracts, because they did not meet the inclusion criteria, or because the trials were not relevant to the review objectives. See [Figure 1](#) for the amended PRISMA trial flow diagram. After screening the full-text of the selected publications, five trials (seven publications) met the inclusion criteria. All trials were published in English.

Figure 1. Study flow diagram

Included studies

A detailed description of the characteristics of included studies is presented elsewhere (see [Characteristics of included studies](#); [Appendix 4](#); [Appendix 5](#); [Appendix 6](#); [Appendix 7](#)). The following is a succinct overview.

Source of data

Using the literature search strategy, we identified 1229 publications: 52 in CENTRAL, 362 in MEDLINE, 793 in Embase, 8 in the WHO ICTRP, and 14 in ClinicalTrials.gov. After removal of duplicates, we had 1069 publications to screen.

Comparisons

One trial included six bilateral and nine monolateral adrenalectomies, performed according to the two techniques, laparoscopic retroperitoneal adrenalectomy (LRPA) or laparoscopic transperitoneal adrenalectomy (LTPA), assigned in a randomised fashion ([Fernández-Cruz 1996](#)). All participants were included in the analysis for all-cause mortality, all-cause morbidity, adverse events, and postoperative parameters (time periods, unwanted effects). For operative parameters (duration of surgery, operative blood loss, intraoperative bleeding, and conversion to open surgery), post-operative parameters (pneumothorax, haemothorax, chest infection, pleural effusion, splenic injury, abdominal abscess), and socioeconomic effects, only participants undergoing monolateral procedures were taken into consideration. All the other trials compared only monolateral adrenalectomies

performed either by LRPA or LTPA, assigned in a randomised fashion.

Overview of trial populations

A total of 244 individuals participated in the five trials, 127 participants were randomised to LRPA, and 117 to LTPA. Almost all randomised participants finished the trials. Five participants were lost at follow-up before the five-year deadline in [Barczynski 2014](#). Only two trials reported sample size calculation ([Barczynski 2014](#); [Chai 2017](#)). The number of recruited participants ranged from 15 ([Fernández-Cruz 1996](#)), to 65 ([Barczynski 2014](#)).

Trial design

Trials were randomised controlled trials (RCTs), but only one declared a parallel group superiority design ([Barczynski 2014](#)). All trials were monocentric. Only one trial declared it was double-blinded, for participants and personnel ([Barczynski 2014](#)). One trial did not declare the time of recruitment ([Fernández-Cruz 1996](#)), while the four others reported recruitment between 1997 and 2012. The mean duration of the intervention ranged between 51 ([Barczynski 2014](#)) and 128 minutes ([Mohammadi-Fallah 2013](#)) in the LRPA group, and 60 ([Chai 2017](#)) and 130 minutes ([Rubinstein 2005](#)) in the LTPA group. The mean duration of follow-up ranged from 9 ([Fernández-Cruz 1996](#); [Mohammadi-Fallah 2013](#)) to 59 months ([Rubinstein 2005](#)). No trials reported a run-in period. No trials were terminated early.

Settings

One trial was conducted in Spain ([Fernández-Cruz 1996](#)), one in Ohio, United States ([Rubinstein 2005](#)), one in Iran ([Mohammadi-Fallah 2013](#)), one in Poland ([Barczynski 2014](#)) and one in South Korea ([Chai 2017](#)). Four of the trials were conducted at academic institutions ([Barczynski 2014](#); [Chai 2017](#); [Fernández-Cruz 1996](#); [Mohammadi-Fallah 2013](#)). No trial was performed in an outpatient setting.

Participants

Participants required an adrenalectomy for a variety of diseases, including aldosterone-producing adenomas, pheochromocytoma, Cushing's disease, Cushing's adenoma, non-functional adenomas, metastasis, adrenal carcinoma, and leiomyosarcoma. Eighty-nine (36%) participants came from low- and middle-income countries, such as Iran and Poland ([Barczynski 2014](#); [Mohammadi-Fallah 2013](#)). No trial provided information about ethnic groups. No trial provided information about the duration of the preoperative condition or disease. Surgical procedures were most commonly performed in women (67%). The mean age of participants ranged from 42.2 years ([Mohammadi-Fallah 2013](#)) to 57.5 years ([Rubinstein 2005](#)) in the LRPA group, and from 39.9 years ([Fernández-Cruz 1996](#)) to 57.0 years ([Rubinstein 2005](#)) in the LTPA group. One hundred and eight (44%) procedures were on the right side, 130 (53%) were on the left, and six (3%) were bilateral adrenalectomies. Four trials reported the BMI: [Barczynski](#)

[2014](#) reported a mean of 27.6 kg/m² in the LRPA group compared with 27.3 kg/m² in the LTPA group; [Rubinstein 2005](#) reported a median of 30.4 kg/m² in the LRPA group compared with 29.1 kg/m² in the LTPA group; [Mohammadi-Fallah 2013](#) noted a mean 27.5 kg/m² in the LRPA group compared with 26.7 kg/m² in the LTPA group; [Chai 2017](#) reported a mean of 23.6 kg/m² in the LRPA group compared with 24.2 kg/m² in the LTPA group. Only one trial reported on comorbidities ([Chai 2017](#)).

The main exclusion criteria were: a history of major abdominal surgery, planned bilateral adrenal surgery, adrenal tumour larger than 6 cm or 7 cm in diameter, and age less than 16 years or 18 years. Some trials excluded participants with suspected adrenocortical cancer or metastasis to the adrenal gland, some trials excluded participants with a BMI higher than 40 kg/m², and some trials excluded participants with an indication for bilateral adrenalectomy, which was an inclusion criterion in one trial ([Fernández-Cruz 1996](#)).

Diagnosis

Corticoid and medullary, benign and malignant, functional and silent tumours, or masses of the adrenal gland were assessed by both laboratory and imaging studies. One trial reported a complete endocrinological work-up before surgery, without details (individuals referred by an endocrinologist ([Mohammadi-Fallah 2013](#))); one did not report diagnostic procedures ([Rubinstein 2005](#)).

Laparoscopic retroperitoneal adrenalectomy was compared with laparoscopic transperitoneal adrenalectomy, performed with either a lateral approach or an anterior approach.

No trial reported treatment before the start of the trial.

Outcomes

[Barczynski 2014](#) and [Chai 2017](#) explicitly stated primary and secondary endpoints in the publication. The defined primary outcome was duration of surgery.

Excluded studies

We excluded 32 trials after careful evaluation of the full publication and record. The main reason for exclusion was that trials did not compare laparoscopic retroperitoneal adrenalectomy with laparoscopic transperitoneal adrenalectomy. There was one retrospective cohort study, with participants who underwent single incision laparoscopic surgery ([Barbaros 2014](#)).

Risk of bias in included studies

For details on the risk of bias of the included trials see [Characteristics of included studies](#). For an overview of review authors' judgements about each risk of bias item for individual trials and across all trials see [Figure 2](#) and [Figure 3](#). We investigated performance bias, detection bias, and attrition bias on an outcome level.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included trials (blank cells indicate that the particular outcome was not measured in some studies)

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial (blank cells indicate that the trial did not measure that particular outcome)

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): all-cause mortality	Blinding of participants and personnel (performance bias): morbidity	Blinding of participants and personnel (performance bias): health-related quality of life	Blinding of participants and personnel (performance bias): operative parameters	Blinding of participants and personnel (performance bias): postoperative parameters	Blinding of participants and personnel (performance bias): socioeconomic effects	Blinding of outcome assessment (detection bias): all-cause mortality	Blinding of outcome assessment (detection bias): morbidity	Blinding of outcome assessment (detection bias): health-related quality of life	Blinding of outcome assessment (detection bias): operative parameters	Blinding of outcome assessment (detection bias): postoperative parameters	Blinding of outcome assessment (detection bias): Socioeconomic effects	Incomplete outcome data (attrition bias): all-cause mortality	Incomplete outcome data (attrition bias): morbidity	Incomplete outcome data (attrition bias): health-related quality of life	Incomplete outcome data (attrition bias): operative parameters	Incomplete outcome data (attrition bias): postoperative parameters	Incomplete outcome data (attrition bias): Socioeconomic effects	Selective reporting (reporting bias)	Other bias
Barczynski 2014	+	?		+		+	+	+		+		+	+	+		+		+	+	?	?	+
Chai 2017	?	?	+	-		+	?	?	+	-		+	?	?	+	+		+	+	+	+	+
Fernández-Cruz 1996	?	?		-		+	?	?		-		+	?	?		+		+	+	+	?	+
Mohammadi-Fallah 2013	+	?	+	-		+	?	?	+	-		+	?	?	+	+		+	+	+	+	+
Rubinstein 2005	+	?	+	-		+	?	?	+	-		+	?	?	+	+		+	+	+	+	+

Allocation

Two trials reported unclear methods for random sequence generation, and we rated them as unclear risk of bias (Chai 2017; Fernández-Cruz 1996). No trial described the method of allocation concealment adequately.

Blinding

Only one trial explicitly reported that it blinded the participants and personnel, describing the methods used to achieve blinding (Barczynski 2014). This trial also provided adequate details about blinding the outcome assessors.

Incomplete outcome data

One trial described the numbers of participants who discontinued the trial; four participants were lost to follow-up (Barczynski 2014). No publication mentioned the use of an intention-to-treat analysis. None of the included trials provided detailed descriptions of participants' withdrawals or reasons underpinning them. No trial had attrition rates that would probably have had an impact on the effect estimates.

Selective reporting

According to the Outcome Reporting Bias In Trials (ORBIT) classification, none of the included trials had a high risk of reporting bias.

Other potential sources of bias

We did not detect any additional risk of bias.

Effects of interventions

See: [Summary of findings for the main comparison Laparoscopic retroperitoneal adrenalectomy compared to laparoscopic transperitoneal adrenalectomy for adrenal tumours in adults](#)

Baseline characteristics

For details of baseline characteristics, see [Appendix 5](#) and [Appendix 6](#).

Primary outcomes

All-cause mortality

Three trials provided data on deaths from any cause ([Chai 2017](#); [Mohammadi-Fallah 2013](#); [Rubinstein 2005](#)). Two trials reported no deaths, in [Rubinstein 2005](#) four participants died in the LRPA group, and one participant in the LTPA group within six years of follow-up (low-certainty evidence; [Analysis 1.1](#)).

Early and late morbidity

Because all-cause morbidity was not reported in the trials, we analysed early and late morbidity, and included specific adverse events (e.g. liver injury, splenic injury, vascular injury, pneumothorax or haemothorax, massive subcutaneous emphysema, surgical access site herniation) under these outcome measures.

For early morbidity (usually reported within 30 to 60 days after surgery), the results were inconclusive between the two techniques (risk ratio (RR) 0.56, 95% confidence interval (CI) 0.27 to 1.16; $P = 0.12$; 5 trials, 244 participants; very low-certainty evidence; [Analysis 1.2](#)). Nine out of 127 participants (7.1%) in the LRPA group, compared with 16 out of 117 participants (13.7%) in the LTPA group, experienced specific adverse events (superficial wound infection, dehiscent wound necessitating closure, massive subcutaneous emphysema, haematoma, fever, transient hypoaesthesia of the abdominal wall, postoperative ileus, atrial fibrillation, tachyarrhythmia requiring medication, systolic blood pressure more than 200 mmHg, pneumonia, noninfectious diarrhoea, urinary retention and urinary tract infection).

LRPA resulted in less late morbidity, measured at the latest available follow-up, than LTPA (RR of 0.12, 95% CI 0.01 to 0.92; $P = 0.04$; 3 trials, 146 participants; very low-quality evidence; [Analysis 1.2](#)). None of the 78 participants in the LRPA group, compared with 7 of the 68 participants (10.3%) in the LTPA group experienced events, such as incisional hernia.

Secondary outcomes

Operative parameters

Duration of surgery

All trials reported this outcome. The mean difference (MD) between LRPA and LTPA duration of surgery was inconclusive (MD 0.7 min; 95% CI -20.0 to 21.3; $P = 0.95$; 5 trials, 250 participants; [Analysis 1.3](#)).

Intraoperative bleeding.

No trials measured this outcome.

Operative blood loss

All trials reported this outcome. The mean difference between LRPA and LTPA blood loss was inconclusive (MD -13 mL, 95% CI -32 to 5; $P = 0.17$; 5 trials, 250 participants; [Analysis 1.4](#)).

Conversion to open surgery

The risk of converting to open surgery was inconclusive between LRPA and LTPA (RR 1.72, 95% CI 0.31 to 9.62; $P = 0.54$; 4 trials, 228 participants; [Analysis 1.5](#)).

Postoperative parameters

Time to oral fluid or food intake

Those who had a LRPA were able to take oral fluids or food earlier than those who had a LTPA (MD -8.6 hours, 95% CI -13.5 to -3.7; $P = 0.0006$; 2 trials, 89 participants; [Analysis 1.6](#)).

Time to ambulation

Those who had a LRPA were able to ambulate more quickly than those who had a LTPA (MD -5.4 hours, 95% CI -6.8 to -4; $P < 0.0001$; 2 trials, 89 participants; [Analysis 1.7](#)).

Chest infection or pleural effusion

[Barczynski 2014](#) reported this outcome in one participant per group ([Analysis 1.8](#)). In [Mohammadi-Fallah 2013](#), no participant had this outcome.

Abdominal abscess

[Barczynski 2014](#) reported this outcome in one participant in the LTPA group ([Analysis 1.8](#)). In [Mohammadi-Fallah 2013](#), no participant had this outcome.

Health-related quality of life

No trial reported health-related quality of life.

Socioeconomic effects

Time to return to normal activities

The results were inconclusive between the two techniques for the time it took participants to return to normal activities, which were ambiguously defined (MD -1.3 days, 95% CI -5.4 to 2.8; $P = 0.52$; 3 trials, 102 participants; very low-quality evidence; [Analysis 1.9](#)).

Length of hospital stay

There were inconclusive results for length of hospital stay between the two techniques (MD -0.36 days, 95% CI -1.16 to 0.44; $P = 0.37$; 5 trials, 250 participants; [Analysis 1.9](#)).

Subgroup analyses

We did not perform subgroups analyses because there were not enough trials to estimate effects in various subgroups.

Sensitivity analyses

We performed sensitivity analyses by examining each outcome using fixed-effects and random-effects models (data not shown). There were inconclusive differences between models. Similarly, we examined how varying the effect size statistic, using odds ratio or risk ratio, influenced trial outcomes (data not shown). Again, we found inconclusive differences between effect size measures.

Assessment of reporting bias

We did not draw funnel plots due to limited number of trials ($N = 5$).

Trials awaiting classification

We found three RCTs comparing LRPA and LTPA, which we categorised as 'awaiting classification'. One completed trial was registered in ClinicalTrials.gov ([NCT02618694](#)) without results and no associated publication, and two trials were only published as conference abstracts ([Abou 2016](#); [Grubnik 2016](#)).

DISCUSSION

Summary of main results

A systematic review of the literature identified five randomised controlled trials (RCTs) comparing the effects of laparoscopic retroperitoneal adrenalectomy (LRPA) with laparoscopic transperitoneal adrenalectomy (LTPA) for adrenal tumours in adults (Barczynski 2014; Chai 2017; Fernández-Cruz 1996; Mohammadi-Fallah 2013; Rubinstein 2005). The five trials showed some heterogeneity in surgical approaches.

Of our key, or primary, outcome measures, no events were reported for all-cause mortality, while one trial reported few events for late morbidity. Contrary to early morbidity, LRPA reported fewer late morbidity events than LTPA, but we are uncertain about this result due to very low-certainty evidence.

Of our secondary outcomes, the results were inconclusive between groups in the analysis of operative parameters (duration of surgery, operative blood loss, conversion to open surgery). For our postoperative parameter time to oral fluid or food intake, we noted an advantage of LRPA, but only two trials reported on this outcome. No trials reported on health-related quality of life.

Overall completeness and applicability of evidence

There was some heterogeneity regarding the surgical techniques used by the different trial authors, especially in indications for surgery. No trial evaluated the experience level and skills of the surgeons.

Quality of the evidence

We evaluated the certainty of the evidence using the GRADE approach, which also considers risk of bias. No trial was at low risk of selection bias, because there was insufficient information about allocation concealment. We downgraded the certainty of the evidence for all-cause mortality, because of the small number of trials and low number of events. Blinding of participants and personnel was difficult; only Barczynski 2014 attempted blinding of trial participants and personnel, but it is likely that the blinding could have been broken in the postsurgical period. For early and late morbidity, we downgraded the evidence to very low quality due to the small number of trials and low number of participants. As the certainty of the evidence varied from low to very low, readers should interpret the results with caution.

Potential biases in the review process

Despite extensive search efforts, we might have overlooked unpublished data, especially regarding the Asian literature. Information, such as the experience of the surgeon performing the adrenalectomy would have been essential for the interpretation of the results, but was not available.

Agreements and disagreements with other studies or reviews

A recent systematic review, based on retrospective studies, found that many studies showed that LRPA was superior, or at least comparable to LTPA, in operation time, pain score, blood loss, hospitalisation, complications rates, and return to normal activity (Conzo 2016). However LTPA appeared to be as safe as LRPA, with a similar low morbidity rate. These results are in line with the results of two previous systematic reviews and meta-analyses that reported comparable outcomes between the two techniques (Constantinides 2012; Nigri 2013). Our results, based on five RCTs, showed that long-term morbidity, time to ambulation, and time to oral fluid or food intake might be reduced following laparoscopic retroperitoneal adrenalectomy.

AUTHORS' CONCLUSIONS

Implications for practice

The body of evidence on laparoscopic retroperitoneal adrenalectomy compared with laparoscopic transperitoneal adrenalectomy is limited. Very low-quality evidence indicates that for relatively small lesions (less than 6 cm to 7 cm), late morbidity might be reduced following the retroperitoneal approach. While no conclusive differences were observed between intervention and comparator groups in the analysis of operative parameters, the analysis of some postoperative parameters, such as the time to oral fluid or food intake and the time to ambulation, may show an advantage for the laparoscopic retroperitoneal adrenalectomy technique. All results have to be interpreted with caution, due to risk of bias, small sample sizes, and low number of events. The other findings of our review could only partially address our objectives. In particular, the included trials did not adequately address or report on health-related quality of life.

Implications for research

Long follow-up periods were reported in only two of our included trials, which limits the body of evidence. No trial was powered to analyse all-cause mortality, and none of the trials investigated health-related quality of life. Important data, such as the treatment volume of the surgical centres and the surgeon's level of experience were not reported, although they may play an important role in operative and postoperative outcomes. New trials reporting on these aspects are required.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Barczynski 2014

Methods	Design: parallel randomised controlled clinical trial, randomisation ratio 1:1
Participants	<p>Inclusion criteria: planned unilateral adrenal surgery for a benign tumour up to 7 cm in diameter, non-functioning adrenal tumours between 4 cm and 7 cm, or smaller lesion, which was progressively enlarging</p> <p>Exclusion criteria: diffuse peritonitis in history, major abdominal surgery in history, planned bilateral adrenal surgery, adrenal tumour more than 7 cm in diameter, suspected adrenocortical cancer, metastasis to adrenal gland, previous adrenal surgery, pregnancy or lactation, age less than 18 or more than 80 years, American Society of Anesthesiologists fitness grade IV, and inability to comply with the follow-up protocol.</p> <p>Diagnostic criteria: abdominal spiral computed tomography (CT) and hormonal activity (urinary metoxycatecholamines, diurnal cortisol, dexamethasone suppression test, ACTH, DHEAS, blood ions, serum aldosterone concentration and serum renin activity).</p>
Interventions	<p>Number of trial centres: 1</p> <p>Treatment before trial: not declared</p> <p>Retroperitoneal laparoscopic adrenalectomy operations were performed using the Walz's technique (individuals are positioned on a rectangular support with bent hip joints at a 90-degree angle to maximally open the space between the 12th rib and iliac crest. Three trocars are used for both right and left procedures, which are placed just under the 12th rib, with direct palpation and finger guidance after the dorsal lumbar fascia is digitally perforated. Balloon trocar in place in the middle port, retroperitoneal space insufflation with 20 to 30 mmHg of CO₂. The dissection of the space is completed with blunt dissection of the area underneath the diaphragm, and the fatty tissue above the superior border of the kidney. Dissection of the adrenal gland starts inferiorly in a plane close to the kidney surface. Identification and ligation of the adrenal vein in a medial or inferomedial position with either clips or a haemostatic device. Mobilisation of the gland is completed by dissecting laterally between the diaphragm and the psoas; the superior attachments are divided last).</p> <p>Transperitoneal laparoscopic adrenalectomy operations were performed employing the Gagner's technique (individuals are positioned at a 60 to 90 degree angle with tumour side up, and the table is flexed to maximally open the space between the tip of the 12th rib and the iliac crest. 3 ports for left adrenalectomy and 4 ports for right adrenalectomy (the fourth port is used for liver retraction). During left adrenalectomy, procedural steps include taking down the splenic flexure of the colon, freeing the</p>

Barczynski 2014 (Continued)

splenic ligaments to mobilize the spleen and rotate it medially, and dissecting in the avascular plane between the tail of the pancreas and kidney, and controlling and dividing the adrenal vein as it enters the left renal vein. During right adrenalectomy, procedural steps include mobilisation of the right triangular ligament of the liver, a hockey stick incision between the retroperitoneal attachments of the right lobe of the liver and the lateral border of the IVC, dissection of the lateral edge of the IVC, and taking the right adrenal vein at the takeoff from the IVC. Superior retraction of the liver must be maintained by the assistant throughout the case to aid exposure of the right adrenal. Mobilisation of the gland follows a superior-lateral to medial-inferior progression unless surgeon preference is for taking the adrenal vein early, in which case, an inferior to superior and medial to lateral mobilisation of the gland is preferred).

CO₂ insufflation pressures are 12 mmHg. Intraoperative dissection and haemostasis was achieved in both groups by the ultrasonic harmonic shears (LCSC5 or ACE; Ultracision; Ethicon EndoSurgery, Somerville, NJ). In both groups, the mobilised adrenal gland was removed through the trocar port with a latex endocath bag (Endocatch, USSC Norwalk, CT). In selected cases, the skin incision was extended to allow for removing the intact surgical material (morcellation was not used). The same fascia closure technique was used for laparoscopic retroperitoneal adrenalectomy (LRPA) and laparoscopic transperitoneal adrenalectomy (LTPA) operations using interrupted absorbable sutures and a BERC Facial Closing Instrument (STORZ, Tuttingen, Germany) for all 10 mm trocar sites, whereas 5 mm trocar sites were not closed. Drainage of the wounds was not used.

Outcomes	<p>Composite outcome measures reported: none</p> <p>Primary endpoint: duration of surgery</p> <p>Secondary endpoints: intraoperative blood loss, conversion rate, postoperative pain, prevalence of shoulder tip pain, additional analgesia requests, nausea and vomiting, time to oral intake, time to ambulation, length of hospital stay, total cost of the operation, postoperative complications (including long-term surgical access site herniation and need for hernia repair), and in cases of active tumours, biochemical and clinical cure rate during 5-year follow-up</p>
Study details	<p>Run-in period: none</p> <p>Trial terminated early: no</p> <p>Trials register identifier: NCT01959711</p>
Publication details	<p>Language of publication: English</p> <p>Commercial funding, non-commercial funding, other funding: not declared</p> <p>Publication status: peer-reviewed journal</p>
Stated aim for study	<p>Quote from publication: "The aim of this study was to evaluate the results of PRA versus LTLA in patients with unilateral benign adrenal tumours up to 7 cm in diameter. It was hypothesized that PRA may be superior to LTLA for both short-term and long-term outcomes"</p>
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from publication: "The randomization sequence was generated by a computer. Sequencing was based on permuted blocks of 2 and 3 to balance the number of participants in the treatment groups"
Allocation concealment (selection bias)	Unclear risk	Quote from publication: "Information on the type of intervention remained in consecutively numbered and sealed envelopes that were stored in the operating theatre. An envelope containing the allocation was added to the pa-

Barczynski 2014 (Continued)

		<p>tient's file in the operating room. The envelope was opened and the surgeon performed the assigned intervention."</p> <p>Comment: questionable whether envelopes were opaque</p>
Blinding of participants and personnel (performance bias) morbidity	Low risk	<p>Quote from publication: "Neither of the patients, nurses, or outcomes assessing clinical investigators knew the relevant group assignment. Both the abdomen and lumbar region on the side of the operation were covered with an opaque, large, and air-permeable but water-resistant dressing to conceal the site of the surgical access for the initial 3 postsurgery days"</p> <p>Comment: blinding of trial participants and personnel attempted, but likely that the blinding could have been broken after the 3 postsurgery days</p>
Blinding of participants and personnel (performance bias) operative parameters	Low risk	<p>Quote from publication: "Neither of the patients, nurses, or outcomes assessing clinical investigators knew the relevant group assignment. Both the abdomen and lumbar region on the side of the operation were covered with an opaque, large, and air-permeable but water-resistant dressing to conceal the site of the surgical access for the initial 3 postsurgery days"</p> <p>Comment: blinding of trial participants and personnel attempted but not in the operating room; outcome measure not likely to be influenced by lack of blinding</p>
Blinding of participants and personnel (performance bias) postoperative parameters	Low risk	<p>Quote from publication: "Neither of the patients, nurses, or outcomes assessing clinical investigators knew the relevant group assignment. Both the abdomen and lumbar region on the side of the operation were covered with an opaque, large, and air-permeable but water-resistant dressing to conceal the site of the surgical access for the initial 3 postsurgery days"</p> <p>Comment: blinding of trial participants and personnel attempted, but likely that the blinding could have been broken after the 3 postsurgery days; outcome measure not likely to be influenced by lack of blinding</p>
Blinding of participants and personnel (performance bias) socioeconomic effects	Low risk	<p>Quote from publication: "Neither of the patients, nurses, or outcomes assessing clinical investigators knew the relevant group assignment. Both the abdomen and lumbar region on the side of the operation were covered with an opaque, large, and air-permeable but water-resistant dressing to conceal the site of the surgical access for the initial 3 postsurgery days"</p> <p>Comment: blinding of trial participants and personnel attempted, but likely that the blinding could have been broken after the 3 postsurgery days</p>
Blinding of outcome assessment (detection bias) morbidity	Low risk	<p>Quote from publication: "Neither of the patients, nurses, or outcomes-assessing clinical investigators knew the relevant group assignment"</p> <p>Quote from publication: "The following data were collected by independent clinical investigators during the trial: duration of surgery, intraoperative blood loss, conversion rate, postoperative pain, prevalence of shoulder-tip pain, additional analgesia requests, nausea and vomiting, time to oral intake of clear liquids and solid diet, time to ambulation, length and cost of hospital stay, morbidity, biochemical laboratory values, and clinical disease recovery data"</p> <p>Comment: blinding of outcome assessment attempted, but likely that the blinding could have been broken</p>
Blinding of outcome assessment (detection bias) operative parameters	Low risk	<p>Quote from publication: "Neither of the patients, nurses, or outcomes-assessing clinical investigators knew the relevant group assignment"</p> <p>Quote from publication: "The following data were collected by independent clinical investigators during the trial: duration of surgery, intraoperative blood loss, conversion rate, postoperative pain, prevalence of shoulder-tip pain, ad-</p>

Barczynski 2014 (Continued)

		ditional analgesia requests, nausea and vomiting, time to oral intake of clear liquids and solid diet, time to ambulation, length and cost of hospital stay, morbidity, biochemical laboratory values, and clinical disease recovery data"
		Comment: blinding of outcome assessment attempted, but likely that the blinding could have been broken; outcome measure not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) postoperative parameters	Low risk	<p>Quote from publication: "Neither of the patients, nurses, or outcomes-assessing clinical investigators knew the relevant group assignment"</p> <p>Quote from publication: "The following data were collected by independent clinical investigators during the trial: duration of surgery, intraoperative blood loss, conversion rate, postoperative pain, prevalence of shoulder-tip pain, additional analgesia requests, nausea and vomiting, time to oral intake of clear liquids and solid diet, time to ambulation, length and cost of hospital stay, morbidity, biochemical laboratory values, and clinical disease recovery data"</p> <p>Comment: blinding of outcome assessment attempted, but likely that the blinding could have been broken; outcome measure not likely to be influenced by lack of blinding</p>
Blinding of outcome assessment (detection bias) Socioeconomic effects	Low risk	<p>Quote from publication: "Neither of the patients, nurses, or outcomes-assessing clinical investigators knew the relevant group assignment"</p> <p>Quote from publication: "The following data were collected by independent clinical investigators during the trial: duration of surgery, intraoperative blood loss, conversion rate, postoperative pain, prevalence of shoulder-tip pain, additional analgesia requests, nausea and vomiting, time to oral intake of clear liquids and solid diet, time to ambulation, length and cost of hospital stay, morbidity, biochemical laboratory values, and clinical disease recovery data"</p> <p>Comment: blinding of outcome assessment attempted, but likely that the blinding could have been broken</p>
Incomplete outcome data (attrition bias) morbidity	Low risk	<p>Quote from publication: "65 patients with complete short-term follow-up (33 in the PRA and 32 in the LTLA group) and 61 patients who were followed-up for 5 years (30 in the PRA and 31 in the LTLA group)"</p> <p>Comment: low attrition rate</p>
Incomplete outcome data (attrition bias) operative parameters	Low risk	<p>Quote from publication: "65 patients with complete short-term follow-up (33 in the PRA and 32 in the LTLA group), and 61 patients who were followed up for 5 years (30 in the PRA and 31 in the LTLA group)"</p> <p>Comment: low attrition rate</p>
Incomplete outcome data (attrition bias) postoperative parameters	Low risk	<p>Quote from publication: "65 patients with complete short-term follow-up (33 in the PRA and 32 in the LTLA group), and 61 patients who were followed up for 5 years (30 in the PRA and 31 in the LTLA group)"</p> <p>Comment: low attrition rate</p>
Incomplete outcome data (attrition bias) Socioeconomic effects	Unclear risk	<p>Quote from publication: "65 patients with complete short-term follow-up (33 in the PRA and 32 in the LTLA group), and 61 patients who were followed up for 5 years (30 in the PRA and 31 in the LTLA group)"</p> <p>Comment: low attrition rate</p>
Selective reporting (reporting bias)	Unclear risk	Comment: primary outcome reported as stated. All secondary outcomes are reported except blood loss. In the protocol of trial, the outcome was blood loss for the duration of hospital stay, but the article reported only the intraop-

Barczynski 2014 (Continued)

erative blood loss. In the article, the outcomes pneumothorax or haemothorax, chest infection, visceral injury, peritonitis or abscess, and neuralgia, as reported in the protocol of the trial, were not mentioned. Deaths were not mentioned.

Other bias	Low risk	Comment: none detected
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Chai 2017

Methods	Design: parallel randomised controlled clinical trial, randomisation ratio 1:1
Participants	<p>Inclusion criteria (from ClinicalTrials.gov):</p> <ul style="list-style-type: none"> • (Publication: age ≥ 18 and < 80) • (Publication: unilateral benign tumour) • Patients who were expected to have benign adrenal disease at preoperative exams • Patients who had pheochromocytoma measured less than 5 cm, and the other benign adrenal tumours less than 7 cm in diameter in preoperative computed tomography (CT) scan • Patients who did not have previous surgery history at the interested quadrant • Patients who was I or II grade in ASA classification (American Society of Anesthesiologists' physical status classification) • Patients who had tolerable liver function and renal function (bilirubin < 2.0 mg/dL, and AST, ALT, serum creatinine within twice of upper normal range, coagulation panel: within normal limit) • Patients whose BMI (body mass index) was less than 35 (publication: ≤ 35) • Patients who had normal cognitive function • Patients who signed the consent paper <p>Exclusion criteria (from ClinicalTrials.gov):</p> <ul style="list-style-type: none"> • Patients who were expected to have malignant or metastatic adrenal tumour at preoperative exams • Patients who had bilateral adrenal tumours • Patients who had another condition, and were to undergo the other operation in the abdomen together with adrenalectomy (publication: necessity of additional surgical procedure) • Pregnant patients • Patients who had active or uncontrolled infection • Patients who had medical problems as below • Uncontrollable hypertension with medication (systolic blood pressure > 150 mmHg or diastolic blood pressure > 100 mmHg) • Angina, congestive heart failure, acute myocardial infection • History of coronary angioplasty or coronary artery bypass graft surgery (publication: history of coronary heart disease) • History of stroke, transient ischaemic attack with sequela (publication: history of cerebrovascular disease) <p>Diagnostic criteria: adrenal protocol computed tomography (CT) was routinely performed before surgery. Biochemical marker screening tests were performed for primary aldosteronism (plasma renin, aldosterone), Cushing syndrome (overnight 1 mg dexamethasone suppression test, serum cortisol, and urine cortisol), and pheochromocytoma (24-hour urine dopamine, epinephrine, metanephrine, norepinephrine, normetanephrine, and VMA). If primary aldosteronism was suspected, adrenal venous sampling was routinely performed for lateralisation, and the patient was prescribed spironolactone for at least 4 weeks preoperatively. If the blood pressure remained uncontrolled, the spironolactone dose was increased, and additional medications were added until systolic and diastolic blood pressures were maintained below 150 mmHg and 100 mmHg, respectively. In pheochromocytoma patients, an alpha-blocker (doxazosin) was prescribed for at least 4 weeks preoperatively. A beta-blocker and a cal-</p>

Chai 2017 (Continued)

cium channel blocker were added in a step-wise manner, until systolic and diastolic blood pressures were maintained below 150 mmHg and 100 mmHg, respectively

Interventions	<p>Number of trial centres: 1 (performed by a single surgeon at Seoul National University Hospital. The surgeon had performed 55 cases of laparoscopic transperitoneal adrenalectomies and 29 cases of posterior transperitoneal adrenalectomies before the start of the trial)</p> <p>Treatment before trial: not reported</p> <p>Retroperitoneal laparoscopic adrenalectomy: the patient was intubated in a patient bed and then turned prone when moved onto the operating table. The procedure was performed with the patient in the prone jackknife position with a moderately bent hip joint. The first incision was made, 2 cm in length, at the lower tip of the 12th rib. The retroperitoneal space was entered under direct vision and widened using the surgeon's index finger. Medial and lateral incisions, 5 mm in length, were made just lateral to the erector spinae muscles, and at the lower tip of the 11th rib, respectively. Trocars were introduced through the medial and lateral incisions under the guidance of the index finger, inserted through the first incision. A 12 mm balloon trocar was then inserted through the first incision. The medial port was used as a camera port. Operative procedures were performed as described by Walz et al. Arterial lines were routinely used in all patients and central venous lines were used in pheochromocytoma patients</p> <p>Transperitoneal laparoscopic adrenalectomy: the patient was placed in the lateral decubitus position, affected side up, on a vacuum bean bag. Then, the operative bed was flexed at the waist to 80°. The operative procedures were performed as described in the literature, with the exception that 3 ports were used on the left side and four on the right</p>	
Outcomes	<p>Composite outcome measures reported: no</p> <p>Primary endpoint: operative time</p> <p>Secondary endpoints: blood loss, intraoperative haemodynamic stability, postoperative pain, recovery of bowel movement, complication rates</p>	
Study details	<p>Run-in period: none</p> <p>Trial terminated early: no</p> <p>Trials register identifier: NCT01676025</p>	
Publication details	<p>Language of publication: English</p> <p>Commercial funding, non-commercial funding, other funding: not reported</p> <p>Publication status: peer-reviewed journal</p>	
Stated aim for study	<p>Quote from publication: "... compare the surgical outcomes of LTPA and LRPA in patients with adrenal gland adenomas"</p>	
Notes	-	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote from publication: "Web-based randomization"; "... patients were randomized to either the LTPA group or the LRPA group in a 1:1 ratio by randomized block design, with block sizes of 4 and 6. The type of intervention was determined on preoperative day 1"</p> <p>Comment: insufficient information about the sequence generation process</p>

Chai 2017 (Continued)

Allocation concealment (selection bias)	Unclear risk	Comment: no details
Blinding of participants and personnel (performance bias) all-cause mortality	Low risk	Quote from publication: "... the participants in this study were not blinded as to which procedure was performed" Comment: outcome measure not likely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) morbidity	High risk	Quote from publication: "... the participants in this study were not blinded as to which procedure was performed" Comment: outcome measure potentially influenced by lack of blinding
Blinding of participants and personnel (performance bias) operative parameters	Low risk	Quote from publication: "... the participants in this study were not blinded as to which procedure was performed" Comment: outcome measure not likely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) postoperative parameters	Unclear risk	Quote from publication: "... the participants in this study were not blinded as to which procedure was performed" Comment: outcome measure potentially influenced by lack of blinding
Blinding of participants and personnel (performance bias) socioeconomic effects	Unclear risk	Quote from publication: "... the participants in this study were not blinded as to which procedure was performed" Comment: outcome measure potentially influenced by lack of blinding
Blinding of outcome assessment (detection bias) all-cause mortality	Low risk	Comment: open label trial, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) morbidity	High risk	Comment: open label trial, outcome potentially influenced by lack of blinding
Blinding of outcome assessment (detection bias) operative parameters	Low risk	Comment: open label trial, outcome not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) postoperative parameters	Unclear risk	Comment: open label trial, outcome potentially influenced by lack of blinding
Blinding of outcome assessment (detection bias) Socioeconomic effects	Unclear risk	Comment: open label trial, outcome potentially influenced by lack of blinding
Incomplete outcome data (attrition bias) all-cause mortality	Low risk	Comment: only 1 participant refused follow-up
Incomplete outcome data (attrition bias) morbidity	Low risk	Comment: only 1 participant refused follow-up
Incomplete outcome data (attrition bias)	Low risk	Comment: only 1 participant refused follow-up

Chai 2017 (Continued)

operative parameters

Incomplete outcome data (attrition bias) postoperative parameters	Low risk	Comment: only 1 participant refused follow-up
Incomplete outcome data (attrition bias) Socioeconomic effects	Low risk	Comment: only 1 participant refused follow-up
Selective reporting (reporting bias)	Low risk	Comment: no substantial differences between information in ClinicalTrials.gov and the publication (see Appendix 7)
Other bias	Low risk	Comment: none detected

Fernández-Cruz 1996

Methods	Design: parallel randomised controlled clinical trial, randomisation ratio 1:1
Participants	<p>Inclusion criteria: Cushing's syndrome, Cushing disease, Cushing adenoma, age > 16 yrs, informed consent</p> <p>Exclusion criteria: none declared</p> <p>Diagnostic criteria: elevated plasma cortisol levels with loss of diurnal rhythm, low-dose dexamethasone suppression test positive, urinary excretion of 17-hydroxycorticosteroids and 17-ketosteroid, plasma adrenocorticotrophic hormone measured by radioimmunoassay; in some individuals, petrosal venous sinus catheterization was performed; computed tomography scan was used to localise the adrenal tumour in individuals with suspected Cushing's adenoma</p>
Interventions	<p>Number of trial centres: 1</p> <p>Treatment before trial: none declared</p> <p>Flank approach in lateral decubitus position was used in all the participants</p> <p>Retroperitoneal laparoscopic adrenalectomy: 1.5 cm incision midaxillary line below the 12th rib, Muscular layer was split to allow the passage of the finger, and create a retroperitoneal space, insertion of a trocar with an inflated balloon tip. The balloon-tipped trocar was withdrawn and a 10 mm Hasson cannula was inserted, insufflation of the space with CO₂ gas at 12 mmHg. 30° optics insertion and three retroperitoneal 10 mm trocars placement respectively below the costal margin, above the iliac crest, and dorsally under direct vision. For right adrenalectomy, the dissection along the vena cava between the renal vein and the liver identified for transparency through the peritoneal wall, which was retracted medially; meticulous dissection separated the adrenal gland from the attachments to the vena cava, and all vascular elements were divided between two clips. For left adrenalectomy, adrenal gland visualisation, dissection of the infero-medial border of the gland, localisation of the renal vein. At this point, the adrenal veins come to view, where they are transected with two clips. The superior adrenal vessels are left in the final dissection for ligature with clips.</p> <p>Transperitoneal laparoscopic adrenalectomy: CO₂ insufflation in the subcostal area with a Veress needle at up to 12 mmHg. Placement of one trocar (10 mm) in the right or left subcostal area at the level of the anterior axillary line and three more (10 mm) on each side were inserted under direct vision in the flank, under the 12th rib, and dorsally. 30° optics inserted.</p> <p>Right adrenal gland was first exposed with sectioning of the right triangular ligament of the liver and retraction of the right lobe of the liver medially. The vena cava was exposed, and the renal vein was identified as a landmark; the dissection then proceeded in a cephalad direction, visualising the adrenal veins that issue directly from the vena cava in a parallel manner. All vessels were sealed with two clips.</p>

Fernández-Cruz 1996 (Continued)

Operative exposure of the left adrenal gland started by reflection of the splenic flexure of the colon downward and division of the avascular splenocolic ligament. The spleen was mobilised by means of a lateral peritoneal incision up to the superior border, allowing mobilisation of the distal pancreas for good exposure of the Gerota's fascia. Exposition for clipping and division of the left adrenal vein entering the superior part of the renal vein were performed. The superior pole of the gland was dissected, and the left adrenal arteries were secured with clips and transected. After bilateral adrenalectomy or right or left adrenalectomy for Cushing's adenoma, a sterile plastic bag was used for adrenal or tumour removal through the anterior trocar site

Outcomes	Composite outcome measures reported: none No primary or secondary outcome stated The following parameters were reported: operative time, estimated blood loss, length of hospital stay, postoperative analgesic requirements, and the time needed to achieve normal activity	
Study details	Run-in period: none Trial terminated early: no	
Publication details	Language of publication: English Commercial funding, non-commercial funding, other funding: not declared Publication status: peer-reviewed journal	
Stated aim for study	Quote from publication: "The aim of this study is to evaluate, in a prospective, randomised study, the feasibility, safety, and outcome of the retroperitoneoscopic approach compared with the laparoscopic transperitoneal approach in patients with Cushing's syndrome"	
Notes	Possible imprecision of the results due to unclear determination of sample size	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from publication: "patients were randomised to have laparoscopic surgery performed with the transperitoneal technique or the retroperitoneal approach" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Quote from publication: "patients were randomised to have laparoscopic surgery performed with the transperitoneal technique or the retroperitoneal approach" Comment: insufficient information about the allocation concealment
Blinding of participants and personnel (performance bias) morbidity	High risk	Comment: no information, outcome measure potentially influenced by lack of blinding
Blinding of participants and personnel (performance bias) operative parameters	Low risk	Quote from publication: "The following parameters were reported: operative time, estimated blood loss, [...]". Comment: no information, outcome measure unlikely to be influenced by lack of blinding

Fernández-Cruz 1996 (Continued)

Blinding of participants and personnel (performance bias) postoperative parameters	Unclear risk	Quote from publication: "The following parameters were reported: [...] length of hospital stay, postoperative analgesic requirements, and the time needed to achieve normal activity". Comment: no information, outcome measure potentially influenced by lack of blinding
Blinding of participants and personnel (performance bias) socioeconomic effects	Unclear risk	Comment: no information, outcome measure potentially influenced by lack of blinding
Blinding of outcome assessment (detection bias) morbidity	High risk	Comment: no information, outcome measure potentially influenced by lack of blinding
Blinding of outcome assessment (detection bias) operative parameters	Low risk	Quote from publication: "The following parameters were reported: operative time, estimated blood loss, [...]". Comment: no information, outcome measure unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) postoperative parameters	Unclear risk	Quote from publication: "The following parameters were reported: [...] length of hospital stay, postoperative analgesic requirements, and the time needed to achieve normal activity". Comment: no information, outcome measure potentially influenced by lack of blinding
Blinding of outcome assessment (detection bias) Socioeconomic effects	Unclear risk	Comment: no information, outcome measure potentially influenced by lack of blinding
Incomplete outcome data (attrition bias) morbidity	Low risk	Comment: no missing data
Incomplete outcome data (attrition bias) operative parameters	Low risk	Quote from publication: "The following parameters were reported: operative time, estimated blood loss, [...]". Comment: no missing data
Incomplete outcome data (attrition bias) postoperative parameters	Low risk	Quote from publication: "The following parameters were reported: [...] length of hospital stay, postoperative analgesic requirements, and the time needed to achieve normal activity". Comment: no missing data
Incomplete outcome data (attrition bias) Socioeconomic effects	Low risk	Comment: no missing data
Selective reporting (reporting bias)	Unclear risk	Comment: all parameters stated in the methods section were reported in the results section (operative time, estimated blood loss, length of hospital stay, postoperative analgesic requirements, and the time needed to achieve normal activity)
Other bias	Low risk	Comment: none detected

Mohammadi-Fallah 2013

Methods	Design: parallel randomised controlled clinical trial, randomisation ratio 1:1
Participants	<p>Inclusion criteria: surgical adrenal disease</p> <p>Exclusion criteria: morbid obesity (BMI > 40), previous major abdominal surgery, clinical suspicion of malignancy, tumour size > 6 cm, bilateral adrenalectomy</p> <p>Diagnostic criteria: complete endocrinological work-up before surgery (individuals referred by an endocrinologist)</p>
Interventions	<p>Number of trial centres: 1</p> <p>Treatment before trial: none declared</p> <p>Retroperitoneal laparoscopic adrenalectomy: 15 mm incision under the tip of the 12th rib; underlying muscle and fasciae division with cautery; surgeon's index finger inserted through the incision to create a plane between posterior Gerota's fascia and Psoas fascia; trocar placement; blunt dissection under direct vision using the laparoscope; insufflation of the retroperitoneum; 5 mm trocar placement at the angle of paraspinal muscle at the origin of the 12th rib; 10 mm trocar placement about two finger widths above the iliac crest near the anterior superior iliac spine; dissection, clipping and division of adrenals artery and vein; blunt division of the remaining attachments to the kidney; endoscopic bag placement and specimen extraction; operative field examination for bleeding with a insufflation pressure down to 5 mmHg</p> <p>Transperitoneal laparoscopic adrenalectomy: insufflation of the abdomen; four trocar placement along the costal margin; line of Toldt incision; medial mobilisation of the left or right colon; (Kocher manoeuvre on the right side to dissect away the duodenum; dissection, clipping and division of adrenal artery and vein; blunt division of the remaining attachments to the kidney; endoscopic bag placement and specimen extraction; operative field examination for bleeding with a insufflation pressure down to 5 mmHg)</p>
Outcomes	<p>Composite outcome measures reported: none</p> <p>Primary outcome: convalescence period, defined as the period needed for complete recovery from the physical aftereffects of surgery and return to normal personal jobs</p> <p>Other outcomes: blood loss, operative time, open conversion, analgesic (tramadol) requirement dose, oral intake, ambulation, hospital stay, postoperative pain</p>
Study details	<p>Run-in period: none</p> <p>Trial terminated early: no</p>
Publication details	<p>Language of publication: English</p> <p>Non-commercial funding: Urmia University of Medical Sciences</p> <p>Publication status: peer-reviewed journal</p>
Stated aim for study	Quote from publication: "We report here our prospective, randomised comparison of TLA versus RLA in 24 patients with medium-term follow-up"
Notes	Possible imprecision of the results due to unclear determination of sample size.
Risk of bias	
Bias	Authors' judgement Support for judgement

Mohammadi-Fallah 2013 (Continued)

Random sequence generation (selection bias)	Low risk	Quote from publication: "Patients were prospectively randomised by a computer-generated program"
Allocation concealment (selection bias)	Unclear risk	Comment: no information
Blinding of participants and personnel (performance bias) all-cause mortality	Low risk	Comment: no information, outcome measure unlikely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) morbidity	High risk	Comment: no information, outcome measure potentially influenced by lack of blinding
Blinding of participants and personnel (performance bias) operative parameters	Low risk	Quote from publication: "The primary surgeon was informed about the pre-selected laparoscopic approach for each individual patient in the operating room, just before the surgery. Intraoperative data were documented by the surgeon in the operating room immediately at the end of the procedure, using a previously designed data sheet. Information that was analysed included [...] intraoperative outcomes." Comment: outcome measure unlikely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) postoperative parameters	Unclear risk	Quote from publication: "The primary surgeon was informed about the pre-selected laparoscopic approach for each individual patient in the operating room, just before the surgery. Intraoperative data were documented by the surgeon in the operating room immediately at the end of the procedure, using a previously designed data sheet. Information that was analysed included [...] postoperative outcomes, and pathological adrenal features." Comment: outcome measure potentially influenced by lack of blinding
Blinding of participants and personnel (performance bias) socioeconomic effects	Unclear risk	Quote from publication: "The primary outcome was the convalescence period, defined as the period needed for complete recovery from the physical aftereffects of surgery and return to normal personal jobs." Comment: outcome measure potentially influenced by lack of blinding
Blinding of outcome assessment (detection bias) all-cause mortality	Low risk	Quote from publication: "Intraoperative data were documented by the surgeon in the operating room, immediately at the end of the procedure, using a previously designed data sheet" Comment: no information, outcome measure potentially influenced by lack of blinding
Blinding of outcome assessment (detection bias) morbidity	High risk	Quote from publication: "Intraoperative data were documented by the surgeon in the operating room immediately at the end of the procedure using a previously designed data sheet" Comment: no information, outcome measure potentially influenced by lack of blinding
Blinding of outcome assessment (detection bias) operative parameters	Low risk	Quote from publication: "Intraoperative data were documented by the surgeon in the operating room, immediately at the end of the procedure, using a previously designed data sheet" Comment: no information, outcome measure unlikely to be influenced by lack of blinding

Mohammadi-Fallah 2013 (Continued)

Blinding of outcome assessment (detection bias) postoperative parameters	Unclear risk	<p>Quote from publication: "Intraoperative data were documented by the surgeon in the operating room, immediately at the end of the procedure, using a previously designed data sheet"</p> <p>Comment: no information, outcome measure potentially influenced by lack of blinding</p>
Blinding of outcome assessment (detection bias) Socioeconomic effects	Unclear risk	<p>Quote from publication: "The primary outcome was the convalescence period, defined as the period needed for complete recovery from the physical aftereffects of surgery and return to normal personal jobs."</p> <p>Comment: no information, outcome measure potentially influenced by lack of blinding</p>
Incomplete outcome data (attrition bias) all-cause mortality	Low risk	Comment: outcome evaluated in each individual
Incomplete outcome data (attrition bias) morbidity	Low risk	Comment: outcome evaluated in each individual
Incomplete outcome data (attrition bias) operative parameters	Low risk	Comment: outcome evaluated in each individual
Incomplete outcome data (attrition bias) postoperative parameters	Low risk	Comment: outcome evaluated in each individual
Incomplete outcome data (attrition bias) Socioeconomic effects	Low risk	<p>Quote from publication: "The primary outcome was the convalescence period, defined as the period needed for complete recovery from the physical aftereffects of surgery and return to normal personal jobs."</p> <p>Comment: outcome evaluated in each individual</p>
Selective reporting (reporting bias)	Low risk	Comment: the protocol was not available; all parameters stated in the methods section were reported in the result section
Other bias	Low risk	Comment: none detected

Rubinstein 2005

Methods	Design: parallel randomised controlled clinical trial, randomisation ratio: 1:1
Participants	<p>Inclusion criteria: surgical adrenal disease</p> <p>Exclusion criteria: age > 80 yrs, BMI > 40, bilateral adrenalectomy, significant prior abdominal surgery in the quadrant of interest</p> <p>Diagnostic criteria: not declared</p>
Interventions	<p>Number of trial centres: 1</p> <p>Treatment before trial: not declared</p> <p>Retroperitoneal laparoscopic adrenalectomy: individual positioned in lateral decubitus (full flank), the operating table was then flexed; horizontal 1.5 cm to 2 cm transverse skin incision just below the</p>

Rubinstein 2005 (Continued)

tip of the last (12th) rib; dissection with the index fingertip to create a space for balloon dilator; balloon dilatation to allow direct access to the adrenal gland; a 10 mm blunt-tip Hasson's trocar was placed as the primary port; the CO₂ pneumoretroperitoneum was established (15 mmHg), and a 30° 10 mm laparoscope was inserted; usually two, and rarely three, secondary ports were placed (the anterior port was inserted near the anterior axillary line at least 3 cm cephalad to the iliac crest; a posterior port was inserted at the junction of the lateral border of the erector spinae muscle with the undersurface of the 12th rib; rarely, a fourth port (2 mm) may be required at the level of the primary port in the anterior axillary line for retraction of the adrenal gland and kidney in an anterior direction).

Transperitoneal laparoscopic adrenalectomy: individual positioning in a semilateral position with extension of the lateral abdominal wall of the affected side; four 10 mm trocars were placed for a left adrenalectomy; on the right side, a 5 mm trocar was added to lift up the liver near the xiphoid process; the first trocar was inserted lateral to the umbilicus by the open laparoscopic procedure under direct vision to prevent accidental injury to the bowels or large vessels; pneumoperitoneum creation with carbon dioxide gas at 14 mmHg to 15 mmHg for insertion of the other trocars; the pressure was reduced to 8 mmHg to 10 mmHg at the beginning of the intraperitoneal procedure after the insertions were complete; on the left side, the peritoneum was incised on the white line of Toldt lateral to the descending colon, which was then retracted medially above the anterior leaf of Gerota's fascia; Gerota's fascia was opened just above the left renal vein to expose the inferior adrenal vein and adrenal gland; the inferior adrenal vein was divided between clips, and the fatty tissue and remaining vessels around the adrenal gland were then divided between clips by electro cauterization or scissors; division of a few superior adrenal veins to free the adrenal gland; on the right side, the adrenal gland usually appeared through the peritoneum when the liver was lifted up; the hepatocolic ligament and peritoneum were incised to expose the anterior surface of the gland, which then was dissected inferiorly, laterally posteriorly, and finally medially, with division of the inferior adrenal vessels; the middle adrenal vein was excised next from the inferior vena cava; then the narrow superior adrenal vessels were excised; the adrenal gland was trapped in an Endopouch® (Ethicon, Cincinnati, OH) and removed from the abdominal cavity through the largest port; the first trocar port made in the open laparoscopic procedure (port A) was closed in two layers: the anterior rectal sheath and the skin; at the other port sites, the skin and subcutaneous layer were closed in a single layer.

Outcomes	Composite outcome measures reported: no Outcome reported: median operative time, median estimated blood loss, median specimen weight, number of open conversion; median analgesic requirement, median days to oral intake, median days to ambulation, median days hospital stay; complications, median convalescence, number of deaths	
Study details	Run-in period: none Trial terminated early: none	
Publication details	Language of publication: English Commercial funding, non-commercial funding, other funding: not declared Publication status: peer-reviewed journal	
Stated aim for study	Quote from publication: "Report our prospective, randomised, single institution comparison of transperitoneal vs retroperitoneal laparoscopic adrenalectomy in 57 consecutive patients with intermediate-term follow-up"	
Notes	Possible imprecision of the results due to unclear determination of sample size	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from publication: "Patients were prospectively randomised by a computer-generated program"

Rubinstein 2005 (Continued)

Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information about allocation concealment
Blinding of participants and personnel (performance bias) all-cause mortality	Low risk	<p>Quote from publication: "The primary surgeon was informed about the pre-selected laparoscopic approach for each individual patient in the operating suite, immediately prior to positioning the patient for surgery"</p> <p>Comment: no information, outcome measure unlikely to be influenced by lack of blinding</p>
Blinding of participants and personnel (performance bias) morbidity	High risk	<p>Quote from publication: "The primary surgeon was informed about the pre-selected laparoscopic approach for each individual patient in the operating suite, immediately prior to positioning the patient for surgery"</p> <p>Comment: no information, outcome measure potentially influenced by lack of blinding</p>
Blinding of participants and personnel (performance bias) operative parameters	Low risk	<p>Quote from publication: "The primary surgeon was informed about the pre-selected laparoscopic approach for each individual patient in the operating suite, immediately prior to positioning the patient for surgery ... Intraoperative data were documented by the primary surgeon in the operating room,, immediately at the end of the procedure, using a statistically validated data sheet. All data were prospectively maintained in a computerised database with Institutional Review Board approval ... Information analysed included [...] intraoperative and postoperative outcomes."</p> <p>Comment: no information, outcome measure unlikely to be influenced by lack of blinding</p>
Blinding of participants and personnel (performance bias) postoperative parameters	Unclear risk	<p>Quote from publication: "The primary surgeon was informed about the pre-selected laparoscopic approach for each individual patient in the operating suite, immediately prior to positioning the patient for surgery ... Intraoperative data were documented by the primary surgeon in the operating room, immediately at the end of the procedure, using a statistically validated data sheet. All data were prospectively maintained in a computerised database with Institutional Review Board approval ... Information analysed included [...] intraoperative and postoperative outcomes."</p> <p>Comment: no information, outcome measure unlikely to be influenced by lack of blinding</p>
Blinding of participants and personnel (performance bias) socioeconomic effects	Unclear risk	Comment: no information, outcome measure potentially influenced by lack of blinding
Blinding of outcome assessment (detection bias) all-cause mortality	Low risk	<p>Quote from publication: "Intraoperative data were documented by the primary surgeon in the operating room, immediately at the end of the procedure, using a validated data sheet"</p> <p>Comment: no information, outcome measure unlikely to be influenced by lack of blinding</p>
Blinding of outcome assessment (detection bias) morbidity	High risk	<p>Quote from publication: "Intraoperative data were documented by the primary surgeon in the operating room, immediately at the end of the procedure, using a validated data sheet"</p> <p>Comment: no information, outcome measure potentially influenced by lack of blinding</p>

Rubinstein 2005 (Continued)

Blinding of outcome assessment (detection bias) operative parameters	Low risk	<p>Quote from publication: "Intraoperative data were documented by the primary surgeon in the operating room, immediately at the end of the procedure, using a validated data sheet"</p> <p>Comment: no information, outcome measure unlikely to be influenced by lack of blinding</p>
Blinding of outcome assessment (detection bias) postoperative parameters	Unclear risk	<p>Quote from publication: "Intraoperative data were documented by the primary surgeon in the operating room, immediately at the end of the procedure, using a validated data sheet"</p> <p>Comment: no information, outcome measure potentially influenced by lack of blinding</p>
Blinding of outcome assessment (detection bias) Socioeconomic effects	Unclear risk	<p>Quote from publication: "Intraoperative data were documented by the primary surgeon in the operating room, immediately at the end of the procedure, using a validated data sheet"</p> <p>Comment: no information, outcome measure potentially influenced by lack of blinding</p>
Incomplete outcome data (attrition bias) all-cause mortality	Low risk	Comment: during the 6-year follow-up, 5 participants died (1 in the transperitoneal, and 4 in the retroperitoneal group)
Incomplete outcome data (attrition bias) morbidity	Low risk	Comment: during the 6-year follow-up, 5 participants died (1 in the transperitoneal, and 4 in the retroperitoneal group)
Incomplete outcome data (attrition bias) operative parameters	Low risk	Comment: during the 6-year follow-up, 5 participants died (1 in the transperitoneal, and 4 in the retroperitoneal group)
Incomplete outcome data (attrition bias) postoperative parameters	Low risk	Comment: during the 6-year follow-up, 5 participants died (1 in the transperitoneal, and 4 in the retroperitoneal group)
Incomplete outcome data (attrition bias) Socioeconomic effects	Low risk	Comment: during the 6-year follow-up, 5 participants died (1 in the transperitoneal, and 4 in the retroperitoneal group)
Selective reporting (reporting bias)	Low risk	Comment: the protocol was not available. All parameters stated in the methods section were reported in the results section
Other bias	Low risk	Comment: none reported

Note: where the judgement is 'Unclear' and the description is blank, the trial did not report that particular outcome.

ACTH: adrenocorticotrophic hormone

AST: aspartate aminotransferase

ALT: alanine transaminase

BMI: body mass index

CT: computed tomography

DHEAS: dehydroepiandrosterone sulfate

IVC: inferior vena cava

LT(L)A: lateral transperitoneal (laparoscopic) adrenalectomy

PRA: posterior retroperitoneoscopic adrenalectomy

RLA: retroperitoneal laparoscopic adrenalectomy

TLA: transperitoneal laparoscopic adrenalectomy

VMA: vanillylmandelic acid

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Barbaros 2014	A retrospective cohort study on participants who underwent single incision laparoscopic surgery
Bonjer 1997	A case-control study comparing open adrenalectomy with laparoscopic retroperitoneal adrenalectomy and laparoscopic transperitoneal adrenalectomy
Bradley 2013	Systematic review of case-series studies including participants affected by adrenal metastases and treated by surgery with different techniques
Desai 2005	A randomised controlled trial on participants who underwent transperitoneal or retroperitoneal laparoscopic radical nephrectomy for renal tumour
Fu 2011	A randomised multicentric trial comparing retroperitoneoscopic partial versus total adrenalectomy for aldosterone producing adenoma
Gockel 2005	A case-control study comparing laparoscopic retroperitoneal adrenalectomy with laparoscopic transperitoneal adrenalectomy
Hallfeldt 2003	A case-control study comparing laparoscopic retroperitoneal adrenalectomy with laparoscopic transperitoneal adrenalectomy
Henry 2002	A retrospective cohort study on participants who underwent laparoscopic transperitoneal adrenalectomy
Hsu 2002	A case-control study comparing participants undergoing bilateral adrenalectomy with either laparoscopic retroperitoneal or laparoscopic transperitoneal technique
Khaira 2004	A randomised, double-blind, placebo controlled trial in which the port sites and hand assist incision were infiltrated with bupivacaine or placebo prior to surgery -- consisting of transperitoneal laparoscopic renal and adrenal surgery
Lee 2012	A case-control study comparing participants undergoing open, robotic, and laparoscopic adrenalectomy with both transperitoneal and retroperitoneal techniques
Lezoche 2002	A case-control study comparing participants undergoing lateral laparoscopic, endoscopic retroperitoneal, or anterior laparoscopic adrenalectomy at three different institutions
Lezoche 2008	A randomised trial comparing participants undergoing the lateral approach and the anterior sub-mesocolic access carrying out left laparoscopic adrenalectomy
Li 2003	A case-control study comparing participants undergoing open or laparoscopic adrenalectomy with either transperitoneal or retroperitoneal technique for the treatment of adrenal tumours
Liao 2001	A case-control study comparing participants undergoing open or laparoscopic adrenalectomy with either transperitoneal or retroperitoneal technique, for the treatment of adrenal tumours
Morino 2004	A randomised trial comparing participants undergoing laparoscopic adrenalectomy and robot-assisted adrenalectomy
Naya 2002	A case-control study comparing participants undergoing laparoscopic adrenalectomy with either transperitoneal or retroperitoneal technique, for the treatment of adrenal tumours
Ramacciato 2008	A case-control study comparing participants undergoing laparoscopic adrenalectomy with either transperitoneal or retroperitoneal technique, for the treatment of adrenal tumours

Study	Reason for exclusion
Ramacciato 2011	A case-control study comparing participants undergoing laparoscopic adrenalectomy with either transperitoneal or retroperitoneal technique, for the treatment of adrenal tumours
Sood 2006	A randomised trial comparing participants undergoing laparoscopic transperitoneal adrenalectomy with either an intraabdominal pressure of 15 mmHg or 8 mmHg to 10 mmHg
Suzuki 2001	A case-control study comparing participants undergoing anterior, lateral, and retroperitoneal laparoscopic adrenalectomy
Tai 2006	A case-control study comparing participants undergoing transperitoneal and retroperitoneal laparoscopic adrenalectomy
Takeda 2000	A case-control study comparing participants undergoing transperitoneal and retroperitoneal laparoscopic adrenalectomy
Tiberio 2008	A randomised trial evaluating cardiovascular instability during open or laparoscopic adrenalectomy for pheochromocytoma
Todorov 2007	A case-control study comparing participants undergoing transperitoneal and retroperitoneal laparoscopic adrenalectomy
Utsumi 2014	A case-series of participants with primary aldosteronism who were treated by unilateral laparoscopic adrenalectomy
Wang 2012	A randomised trial comparing cost-effectiveness of three strategies (adrenalectomy, surveillance, or no follow-up) in participants with a nonfunctional, 4-cm adrenal incidentaloma with no radiographic suspicion of adrenocortical carcinoma
Wu 2013	A randomised trial comparing catecholamines levels in participants undergoing transperitoneal or retroperitoneal for pheochromocytoma, randomly assigned to dissection after ligation or dissection before ligation of the adrenal vein
Yang 2013	A case-series assessing safety and feasibility of a staged laparoscopic training program for beginners with no experience of open technique, to perform laparoscopic adrenalectomy
Zacharias 2006	Review on different techniques of adrenalectomy and case-series presentation on participants undergoing transperitoneal laparoscopic adrenalectomy
Zhang 2009	A case-series assessing safety and feasibility of a staged laparoscopic training program for beginners with no experience of open technique, to perform laparoscopic adrenalectomy
Zografos 2009	Review on laparoscopic surgery techniques for malignant adrenal tumours

Characteristics of studies awaiting assessment *[ordered by study ID]*

Abou 2016

Methods	Randomised controlled trial
Participants	Adults with any benign adrenal masses without local or distant invasion, and children with neuroblastoma; posterior retroperitoneoscopic adrenalectomy 7 participants, anterior transperitoneal adrenalectomy 6 participants

Abou 2016 (Continued)

Interventions	Posterior retroperitoneoscopic adrenalectomy compared with anterior transperitoneal adrenalectomy
Outcomes	Operative time, estimated blood loss, postoperative hospital stay, rate of complications
Study details	Trial was performed in the Alexandria University, Egypt
Publication details	Conference abstract
Stated aim of study	Comparison of the perioperative short-term outcomes of posterior retroperitoneoscopic adrenalectomy versus anterior transperitoneal adrenalectomy
Notes	Publication not yet available

Grubnik 2016

Methods	Randomised controlled trial
Participants	68 participants with tumours of the left adrenal gland; laparoscopic adrenalectomy 35 participants, retroperitoneoscopic adrenalectomy 33 participants
Interventions	Laparoscopic adrenalectomy versus retroperitoneoscopic adrenalectomy for left adrenalectomies
Outcomes	Conversion rate, operative time, time to first oral intake, analgesic requirements, length of hospital stay, postoperative complications
Study details	Trial was performed in the Odessa National Medical University, Ukraine; trial period 2010 to 2015
Publication details	Conference abstract
Stated aim of study	Comparison of the results of laparoscopic adrenalectomy versus retroperitoneoscopic adrenalectomy for left adrenalectomies
Notes	Publication not yet available

NCT02618694

Methods	Parallel randomised controlled trial, double-blind (participant, investigator)
Participants	Participants with functioning or nonfunctioning adrenal adenoma, secondary metastatic adrenal mass, adrenal hyperplasia. Exclusion criteria: cardiovascular disease, pregnancy, locally advanced malignant disease, regional lymph node involvement, vascular malignant invasion, malignant uncontrolled hypertension with pheochromocytoma, need for other simultaneous surgical intervention at the same session
Interventions	Transperitoneal laparoscopic adrenalectomy versus posterior retroperitoneoscopic adrenalectomy
Outcomes	Primary: mean operative time (1 year), mean amount of intraoperative blood loss (1 year), mean days of postoperative hospital stay (1.5 years), rate of complications (1.5 years)

NCT02618694 (Continued)

Secondary: mean of postoperative pain score (1 year), mean of scar cosmetic assessment score (1 year)

Study details	Trial started in April 2016 and was completed in December 2016; performed in the Alexandria Main University Hospital, Egypt (collaborators: Suez Canal University, Ismailia)
Publication details	Registered trial in ClinicalTrials.gov
Stated aim of study	To assess the safety and efficacy of the posterior retroperitoneoscopic adrenalectomy in comparison to the anterior transperitoneal laparoscopic approach
Notes	Publication not yet available; ClinicalTrials.gov-ID: NCT02618694 (responsible party: Ahmed Mohamed Bakr Arabi, Suez Canal University)

DATA AND ANALYSES

Comparison 1. Laparoscopic retroperitoneal adrenalectomy (LRPA) versus laparoscopic transperitoneal adrenalectomy (LTPA)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Early and late morbidity	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Early morbidity	5	244	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.27, 1.16]
2.2 Late morbidity	3	146	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.01, 0.92]
3 Operative parameters: duration of surgery (min)	5	250	Mean Difference (IV, Random, 95% CI)	0.68 [-19.94, 21.29]
4 Operative parameters: blood loss (mL)	5	250	Mean Difference (IV, Random, 95% CI)	-13.06 [-31.55, 5.44]
5 Operative parameters: conversion to open surgery	4	228	Risk Ratio (M-H, Random, 95% CI)	1.72 [0.31, 9.62]
6 Postoperative parameters: time to oral fluid or food intake (hr)	2	89	Mean Difference (IV, Random, 95% CI)	-8.55 [-13.45, -3.66]
7 Postoperative parameters: time to ambulation (hr)	2	89	Mean Difference (IV, Fixed, 95% CI)	-5.41 [-6.77, -4.04]
7.1 Time to ambulation (hr)	2	89	Mean Difference (IV, Fixed, 95% CI)	-5.41 [-6.77, -4.04]
8 Postoperative parameters: chest infection, abdominal abscess	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Chest infection/pleural effusion	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Abdominal abscess	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Socioeconomic effects	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 Time to return to normal activities (days)	3	102	Mean Difference (IV, Random, 95% CI)	-1.33 [-5.43, 2.76]
9.2 Length of hospital stay (days)	5	250	Mean Difference (IV, Random, 95% CI)	-0.36 [-1.16, 0.44]

Analysis 1.1. Comparison 1 Laparoscopic retroperitoneal adrenalectomy (LRPA) versus laparoscopic transperitoneal adrenalectomy (LTPA), Outcome 1 All-cause mortality.

Study or subgroup	LRPA n/N	LTPA n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Rubinstein 2005	4/32	1/25		3.13[0.37,26.24]
Mohammadi-Fallah 2013	0/13	0/11		Not estimable
Chai 2017	0/41	0/42		Not estimable
Favours LRPA 0.01 0.1 1 10 100 Favours LTPA				

Analysis 1.2. Comparison 1 Laparoscopic retroperitoneal adrenalectomy (LRPA) versus laparoscopic transperitoneal adrenalectomy (LTPA), Outcome 2 Early and late morbidity.

Study or subgroup	LRPA n/N	LTPA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Early morbidity					
Fernández-Cruz 1996	0/8	2/7		6.51%	0.18[0.01,3.18]
Rubinstein 2005	1/32	2/25		9.86%	0.39[0.04,4.07]
Mohammadi-Fallah 2013	1/13	1/11		7.69%	0.85[0.06,12.01]
Barczynski 2014	6/33	10/32		68.71%	0.58[0.24,1.41]
Chai 2017	1/41	1/42		7.22%	1.02[0.07,15.84]
Subtotal (95% CI)	127	117		100%	0.56[0.27,1.16]
Total events: 9 (LRPA), 16 (LTPA)					
Heterogeneity: Tau ² =0; Chi ² =0.99, df=4(P=0.91); I ² =0%					
Test for overall effect: Z=1.57(P=0.12)					
1.2.2 Late morbidity					
Rubinstein 2005	0/32	2/25		47.65%	0.16[0.01,3.14]
Mohammadi-Fallah 2013	0/13	0/11			Not estimable
Barczynski 2014	0/33	5/32		52.35%	0.09[0.01,1.53]
Subtotal (95% CI)	78	68		100%	0.12[0.01,0.92]
Total events: 0 (LRPA), 7 (LTPA)					
Heterogeneity: Tau ² =0; Chi ² =0.08, df=1(P=0.78); I ² =0%					
Favours LRPA 0.005 0.1 1 10 200 Favours LTPA

Analysis 1.3. Comparison 1 Laparoscopic retroperitoneal adrenalectomy (LRPA) versus laparoscopic transperitoneal adrenalectomy (LTPA), Outcome 3 Operative parameters: duration of surgery (min). **Analysis 1.4. Comparison 1 Laparoscopic retroperitoneal adrenalectomy (LRPA) versus laparoscopic transperitoneal adrenalectomy (LTPA), Outcome 4 Operative parameters: blood loss (mL).**

Analysis 1.5. Comparison 1 Laparoscopic retroperitoneal adrenalectomy (LRPA) versus laparoscopic transperitoneal adrenalectomy (LTPA), Outcome 5 Operative parameters: conversion to open surgery. **Analysis 1.6. Comparison 1 Laparoscopic retroperitoneal adrenalectomy (LRPA) versus laparoscopic transperitoneal adrenalectomy (LTPA), Outcome 6 Postoperative parameters: time to oral fluid or food intake (hr).** **Analysis 1.7. Comparison 1 Laparoscopic retroperitoneal adrenalectomy (LRPA) versus laparoscopic transperitoneal adrenalectomy (LTPA), Outcome 7 Postoperative parameters: time to ambulation (hr).**

Analysis 1.8. Comparison 1 Laparoscopic retroperitoneal adrenalectomy (LRPA) versus laparoscopic transperitoneal adrenalectomy (LTPA), Outcome 8 Postoperative parameters: chest infection, abdominal abscess. **Analysis 1.9. Comparison 1 Laparoscopic retroperitoneal adrenalectomy (LRPA) versus laparoscopic transperitoneal adrenalectomy (LTPA), Outcome 9 Socioeconomic effects.**

ADDITIONAL TABLES

Table 1. Overview of trial populations

Trial ID (design)	Intervention and comparator	Sample size ^a	Screened/eligible (N)	Randomised (N) [number of adrenalectomies]	Analysed (N)	Finishing trial, short-term follow-up (N)	Randomised finishing study (%)	Follow-up time ^b
Chai 2017 (parallel RCT)	I: posterior retroperitoneoscopic adrenalectomy	" ... sample size ... was calculated for a 5% two-sided significance and 80% power on the basis of mean operative time (80.4 minutes for LRPA and 96 minutes for LTPA) and standard deviation of operative time (12.71 minutes for LRPA and 28.32 minutes for LTPA), which were obtained from a pilot study (data not shown), resulting in 33 patients per group that was divided by 0.864. The final sample size was 42 patients in each group, allowing for a 5% dropout rate"	84 ^b	41	41	41	100	31 months
	C: transperitoneal adrenalectomy			42	42	42	100	
	total:			83	83	83	100	
Barczynski 2014 ^c (parallel RCT)	I: posterior retroperitoneoscopic adrenalectomy	Under the assumption of a 20% reduction in duration of surgery, it was calculated that 24 participants would be required in each treatment arm to give the study a power of 90%; anticipating a 25% loss to follow-up, 32 participants per arm were required in the trial	88	33	33	30	91	5 years
	C: transperitoneal adrenalectomy			32	32	30	94	
	total:			65	65	60	92	
Fernández-Cruz 1996 (parallel RCT)	I: retroperitoneal adrenalectomy	-	-	8 (11)	8	8	100	9 months
	C: transperitoneal adrenalectomy			7 (10)	7	7	100	
	total:			15	15	15	100	

Table 1. Overview of trial populations (Continued)

Mohammedi-Fallah 2013 (parallel RCT)	I: retroperitoneal adrenalectomy	-	-	13	12 ^d	13	100	9 months
	C: transperitoneal adrenalectomy			11	11	11	100	
	total:			24	23	24	100	
Rubinstein 2005 ^e (parallel RCT)	I: retroperitoneal adrenalectomy	-	-	32	32	32	100	6 years
	C: transperitoneal adrenalectomy			25	25	25	100	
	total:			57	57	57	100	
Grand total	All interventions			127				
	All comparators			117				
	All interventions and comparators			244				

- denotes not reported

^aFollow-up under randomised conditions until end of trial (= duration of intervention + follow-up post-intervention or identical to duration of intervention); extended follow-up refers to follow-up of participants once the original trial was terminated, as specified in the power calculation

^bOne participant refused follow-up (a total of 83 participants were eligible for analysis)

^c61 participants completed the 5-year follow-up, 4 participants lost to long-term follow-up (retroperitoneoscopic adrenalectomy: 1 withdrew from trial, 2 unable to communicate; transperitoneal adrenalectomy: 1 unable to communicate)

^dOne participant with open conversion because of "failure to progress"

^e52 participants finished the 6-year follow-up

C: comparator; **I:** intervention; **ITT:** intention-to-treat; **LTPA:** laparoscopic transperitoneal adrenalectomy; **LRPA:** posterior retroperitoneoscopic adrenalectomy ; **N/A:** not applicable; **RCT:** randomised controlled trial

APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials (Cochrane Register of Studies Online)

1. ((transperiton* or retroperiton* or laparoscop* or endoscop*) ADJ7 adrenalectom*):TI,AB,KY
 2. MESH DESCRIPTOR Adrenalectomy
 3. MESH DESCRIPTOR Laparoscopy EXPLODE ALL TREES
 4. #2 AND #3
 5. #1 OR #4
-

MEDLINE Ovid

1. ((transperiton* or retroperiton* or laparoscop* or endoscop*) adj6 adrenalectom*).tw.
 2. Adrenalectomy/ and exp Laparoscopy/
 3. 1 or 2
 - [4.-13. Cochrane Handbook 2008 RCT filter - sensitivity maximizing version, without "drug therapy.fs."]*
 4. randomized controlled trial.pt.
 5. controlled clinical trial.pt.
 6. randomi?ed.ab.
 7. placebo.ab.
 8. randomly.ab.
 9. trial.ab.
 10. groups.ab.
 11. or/4-10
 12. exp animals/ not humans/
 13. 11 not 12
 14. 3 and 13
-

Embase Ovid

1. ((transperiton* or retroperiton* or laparoscop* or endoscop*) adj6 adrenalectom*).tw.
 2. adrenalectomy/ and exp laparoscopy/
 3. 1 or 2
 - [4: Wong 2006 "sound treatment studies" filter – BS version]*
 4. random*.tw. or clinical trial*.mp. or exp health care quality/
 5. 3 and 4
 - [6.-9.TSC Portal filter for exclusion of animal references]*
 6. exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
 7. human/ or normal human/ or human cell/
 8. 6 and 7
 9. 6 not 8
 10. 5 not 9
-

(Continued)

11. limit 10 to embase

ClinicalTrials.gov (Basic Search)

(transperitoneal OR retroperitoneal OR laparoscopic OR endoscopic OR retroperitoneoscopic) AND (adrenalectomy OR adrenalectomies)

ICTRP Search Portal (Standard Search)

transperiton* AND adrenalectom* OR
retroperiton* AND adrenalectom* OR
laparoscop* AND adrenalectom* OR
endoscop* AND adrenalectom*

Appendix 2. 'Risk of bias' assessment

'Risk of bias' domains

1. Random sequence generation (selection bias due to inadequate generation of a randomised sequence)

For each included trial, we will describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

- Low risk of bias: the trial authors achieved sequence generation using computer-generated random numbers or a random numbers table. Drawing of lots, tossing a coin, shuffling cards or envelopes, and throwing dice are adequate if an independent person performed this who was not otherwise involved in the trial. We will consider the use of the minimisation technique as equivalent to being random.
- Unclear risk of bias: insufficient information about the sequence generation process.
- High risk of bias: the sequence generation method was non-random or quasi-random (e.g. sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number; allocation by judgment of the clinician; allocation by preference of the participant; allocation based on the results of a laboratory test or a series of tests; or allocation by availability of the intervention).

2. Allocation concealment (selection bias due to inadequate concealment of allocation prior to assignment)

For each included trial, we will describe the method used to conceal allocation to interventions prior to assignment, and we will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

- Low risk of bias: central allocation (including telephone, interactive voice-recorder, internet-based, and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
- Unclear risk of bias: insufficient information about the allocation concealment.
- High risk of bias: used an open random allocation schedule (e.g. a list of random numbers); assignment envelopes used without appropriate safeguards; alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

We will also evaluate trial baseline data to incorporate assessment of baseline imbalance into the 'Risk of bias' judgment for selection bias ([Corbett 2014](#)).

Chance imbalances may also affect judgments on the risk of attrition bias. In the case of unadjusted analyses, we will distinguish between trials that we rate as being at low risk of bias on the basis of both randomisation methods and baseline similarity, and trials that we judge as being at low risk of bias on the basis of baseline similarity alone ([Corbett 2014](#)). We will reclassify judgements of unclear, low, or high risk of selection bias as specified in [Appendix 5](#).

3. Blinding of participants and trial personnel (performance bias due to knowledge of the allocated interventions by participants and personnel during the trial)

We will evaluate the risk of detection bias separately for each outcome ([Hróbjartsson 2013](#)). We will note whether endpoints were self-reported, investigator-assessed, or adjudicated outcome measures (see below).

(Continued)

- Low risk of bias: blinding of participants and key trial personnel was ensured, and it was unlikely that the blinding could have been broken; no blinding or incomplete blinding, but we judge that the outcome is unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of participants and trial personnel; the trial does not address this outcome.
- High risk of bias: no blinding or incomplete blinding, and the outcome is likely to have been influenced by lack of blinding; blinding of trial participants and key personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

4. Blinding of outcome assessment (detection bias due to knowledge of the allocated interventions by outcome assessment)

We will evaluate the risk of detection bias separately for each outcome ([Hróbjartsson 2013](#)). We will note whether endpoints were self-reported, investigator-assessed, or adjudicated outcome measures (see below).

- Low risk of bias: blinding of outcome assessment is ensured, and it is unlikely that the blinding could have been broken; no blinding of outcome assessment, but we judge that the outcome measurement is unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of outcome assessors; the trial did not address this outcome.
- High risk of bias: no blinding of outcome assessment, and the outcome measurement was likely to have been influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

5. Incomplete outcome data (attrition bias due to amount, nature or handling of incomplete outcome data)

For each included trial or each outcome, or both, we will describe the completeness of data, including attrition and exclusions from the analyses. We will state whether the trial reported attrition and exclusions, and report the number of participants included in the analysis at each stage (compared with the number of randomised participants per intervention and comparator groups). We will also note if the trial reported the reasons for attrition or exclusion, and whether missing data were balanced across groups, or were related to outcomes. We will consider the implications of missing outcome data per outcome, such as high dropout rates (e.g. above 15%), or disparate attrition rates (e.g. difference of 10% or more between trial arms).

- Low risk of bias: no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to introduce bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference) among missing outcomes was not enough to have a clinically relevant impact on observed effect size; appropriate methods, such as multiple imputation, were used to handle missing data.
- Unclear risk of bias: insufficient information to assess whether missing data, in combination with the method used to handle missing data, were likely to induce bias; the trial did not address this outcome.
- High risk of bias: reason for missing outcome data was likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference) among missing outcomes enough to induce clinically-relevant bias in observed effect size; 'as-treated' or similar analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.

6. Selective reporting (reporting bias due to selective outcome reporting)

We will assess outcome reporting bias by integrating the results of the appendix 'Matrix of trial endpoints (publications and trial documents)' ([Boutron 2014](#); [Mathieu 2009](#)), with those of the appendix 'High risk of outcome reporting bias according to the Outcome Reporting Bias In Trials (ORBIT) classification' ([Kirkham 2010](#)). This analysis will form the basis for the judgement of selective reporting.

- Low risk of bias: the trial protocol was available and all the trial's prespecified (primary and secondary) outcomes that were of interest to this review were reported in the prespecified way; the study protocol was unavailable, but it was clear that the published reports included all expected outcomes (ORBIT classification).
- Unclear risk of bias: insufficient information about selective reporting.
- High risk of bias: not all the trial's prespecified primary outcomes were reported; one or more primary outcomes were reported using measurements, analysis methods, or subsets of the data (e.g. subscales) that were not prespecified; one or more reported primary outcomes were not prespecified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the Cochrane Review were reported incompletely, so that we could not enter them in a meta-analysis; the trial report failed to include results for a key outcome that we would expect to have been reported for such a trial (ORBIT classification).

(Continued)

7. Other bias

- Low risk of bias: the trial appeared to be free from other sources of bias.
- Unclear risk of bias: there was insufficient information to assess whether an important risk of bias existed; insufficient rationale or evidence that an identified problem introduced bias.
- High risk of bias: the trial had a potential source of bias related to the specific trial design used; the trial was claimed to be fraudulent; or the trial had some other serious problem.

Appendix 3. Selection bias decisions

Selection bias decisions for trials that reported unadjusted analyses: comparison of results obtained using method details alone with results using method details and trial baseline information^a

Reported randomisation and allocation concealment methods	Risk of bias judgement using methods reporting	Information gained from trial characteristics data	Risk of bias using baseline information and methods reporting
Unclear methods	Unclear risk	Baseline imbalances present for important prognostic variable(s)	High risk
		Groups appear similar at baseline for all important prognostic variables	Low risk
		Limited or no baseline details	Unclear risk
Would generate a truly random sample, with robust allocation concealment	Low risk	Baseline imbalances present for important prognostic variable(s)	Unclear risk^b
		Groups appear similar at baseline for all important prognostic variables	Low risk
		Limited baseline details, showing balance in some important prognostic variables ^c	Low risk
		No baseline details	Unclear risk
Sequence is not truly randomised or allocation concealment is inadequate	High risk	Baseline imbalances present for important prognostic variable(s)	High risk
		Groups appear similar at baseline for all important prognostic variables	Low risk
		Limited baseline details, showing balance in some important prognostic variables ^c	Unclear risk
		No baseline details	High risk

^aTaken from [Corbett 2014](#); judgements highlighted in bold indicate situations in which the addition of baseline assessments would change the judgement about risk of selection bias, compared with using methods reporting alone.

^bImbalance identified that appears likely to be due to chance.

^cDetails for the remaining important prognostic variables are not reported.

Appendix 4. Description of interventions

Trial ID	Intervention	Comparator	Adrenalectomy
Chai 2017	Retroperitoneal adrenalectomy	Transperitoneal adrenalectomy	Unilateral adrenalectomies
Barczynski 2014	Retroperitoneal adrenalectomy	Transperitoneal adrenalectomy	Unilateral total adrenalectomies
Mohammadi-Falah 2013	Retroperitoneal adrenalectomy	Transperitoneal adrenalectomy	Unilateral adrenalectomies
Rubinstein 2005	Retroperitoneal adrenalectomy	Transperitoneal adrenalectomy	Unilateral adrenalectomies
Fernández-Cruz 1996	Retroperitoneal adrenalectomy	Transperitoneal adrenalectomy	Unilateral and bilateral adrenalectomies

Appendix 5. Baseline characteristics (I)

Trial ID	Intervention and comparator	Duration of follow-up	Description of participants	Trial period (year to year)	Country	Setting	Ethnic groups (%)	Duration of disease (mean years (SD))
Chai 2017	I: retroperitoneal adrenalectomy	31.3 months	Individuals with adrenal gland adenomas	2012 to 2016	South Korea	Seoul National University Hospital, Seoul	-	-
	C: transperitoneal adrenalectomy						-	-
Barczynski 2014	I: retroperitoneal adrenalectomy	1, 12, 24, 36, 48, and 60 months after surgery	Individuals with adrenal tumours	2006 to 2008	Poland	Medical College, Jagiellonian University, Krakow	-	-
	C: transperitoneal adrenalectomy							
Mohammadi-Fallah 2013	I: retroperitoneal adrenalectomy	Mean follow-up 9 months	Individuals with surgical adrenal disease	2008 to 2011	Iran	Imam Medical Center, Urmia University	-	-
	C: transperitoneal adrenalectomy							
Rubinstein 2005	I: retroperitoneal adrenalectomy	Mean follow-up 5.9 years	Individuals with surgical adrenal disease	1997 to 1999	USA	Glickman Urological Institute, Cleveland	-	-
	C: transperitoneal adrenalectomy							
Fernández-Cruz 1996	I: retroperitoneal adrenalectomy	Participants with total bilateral adrenalectomy: mean follow-up 9.2 months (SD 6.1)	Individuals with Cushing's syndrome (including Cushing's disease and Cushing's adenoma)	-	Spain	Hospital Clínic, University of Barcelona	-	-
	C: transperitoneal adrenalectomy							
- denotes not reported								
C: comparator; I: intervention; SD: standard deviation								

Appendix 6. Baseline characteristics (II)

Trial ID	Intervention and comparator	Sex (female %)	Age (mean years (SD), or as reported)	BMI (mean kg/m ² (SD), or as reported)	Tumour size (mm) and preoperative diagnosis (number)	Previous abdominal surgery	Lateral location (right side/ left side)	Comorbidities
Chai 2017	I: retroperitoneal adrenalectomy	63	46.4 (11.0)	23.6 (3.0)	Mean 30 (SD 13) Preoperative diagnosis: Aldosteronoma: 16 Cushing syndrome: 10 Pheochromocytoma: 7 Nonfunctioning tumour: 8	Yes (29%)	18/23	Hypertension: 66%
	C: transperitoneal adrenalectomy	67	48.0 (11.4)	24.2 (3.3)	Mean 29 (14) Preoperative diagnosis: Aldosteronoma: 20 Cushing syndrome: 7 Pheochromocytoma: 8 Nonfunctioning tumour: 7	Yes (26%)	18/24	Hypertension: 76%
Barczynski 2014	I: retroperitoneal adrenalectomy	76	47.9	27.6	Mean 39 (10 to 70) Preoperative diagnosis: Aldosteronoma: 7 Glucocorticoid adrenal adenoma: 4 Pheochromocytoma: 8 Nonfunctioning tumour: 14	Yes (not major)	16/17	-
	C: transperitoneal adrenalectomy	72	46.6	27.3	Mean 40 (10 to 65) Preoperative diagnosis: Aldosteronoma: 7 Glucocorticoid adrenal adenoma: 3 Pheochromocytoma: 7 Nonfunctioning tumour: 15	Yes (not major)	15/17	-
Mohammadi-Fallah 2013	I: retroperitoneal adrenalectomy	62	42.2 (median)	27.5 (median)	Median 26 (IQR 20 to 50) Preoperative diagnosis: Aldosteronoma: 1 Pheochromocytoma: 2 Cushing's syndrome: 4	Yes (not major)	8/5	-

(Continued)

Nonfunctioning tumour: 6								
	C: transperitoneal adrenalectomy	55	42.9 (median)	26.7 (median)	Median 29 (IQR 20 to 50) Preoperative diagnosis: Aldosteronoma: 2 Pheochromocytoma: 2 Cushing's syndrome: 3 Nonfunctioning tumour: 4	Yes (not major)	6/5	-
Rubinstein 2005	I: retroperitoneal adrenalectomy	59	57.5 (median)	30.4 (median)	Median 26 (IQR 17 to 49) Preoperative diagnosis: Aldosteronoma: 10 Not specified: 15 Pheochromocytoma: 2 Cushing's syndrome: 3 Metastasis: 1 Adrenal carcinoma: 1	Yes (not major)	9/23	-
	C: transperitoneal adrenalectomy	48	57 (median)	29.1 (median)	Median 27 (IQR 16 to 42) Preoperative diagnosis: Aldosteronoma: 10 Not specified: 5 Pheochromocytoma: 7 Cushing's syndrome: 2 Metastasis: 1 Adrenal carcinoma: 0	Yes (not major)	12/13	-
Fernández-Cruz 1996	I: retroperitoneal adrenalectomy	73	49.9 (17.8)	-	Preoperative diagnosis: 5 adenoma, tumour size: 51 (38 to 75) 6 hyperplasia, , tumour size: 54 (35 to 79)	-	Adenoma: 2/3 Hyperplastic glands: 3/3	-
	C: transperitoneal adrenalectomy	71	39.9 (18.4)	-	Preoperative diagnosis: 4 adenoma, tumour size: 49 (25 to 65) 6 hyperplasia, tumour size: 58 (40 to 72)	-	Adenoma: 1/3	-

Hyperplas-
tic glands:
3/3

(Continued)

- denotes not reported

BMI: body mass index; **C:** comparator; **I:** intervention; **IQR:** interquartile range; **SD:** standard deviation

Appendix 7. Matrix of trial endpoints (publications and trial documents)

Study ID	Endpoints quoted in trial document(s) ^a	Trial results available in trial register	Endpoints quoted in publication(s) ^{b,c}	Endpoints quoted in abstract of publication(s) ^{b,c}
Chai 2017	Source: NCT01676025	No	Primary outcome measure(s): operative time	Primary outcome measure(s): operative time
	Primary outcome measure(s): operation time (participants will be followed until the first visit at outpatient clinic after discharge, an expected average of 3 weeks)			
	Secondary outcome measure(s): pain sensation after surgery (pain score will be described daily during hospitalisation, and also at outpatient clinic after discharge, an expected average of 3 weeks); recovery of bowel movement (participants will be followed for the duration of hospital stay, an expected average of 5 days); wound complication (participants will be followed until the first visit at outpatient clinic after discharge, an expected average of 3 weeks); blood loss during operation (participants will be followed until the first visit at outpatient clinic after discharge, an expected average of 3 weeks); intraoperative haemodynamic status (participants will be followed until the first visit at outpatient clinic after discharge, an expected average of 3 weeks); severe hypertension (systolic blood pressure > 200 mmHg), severe hypotension (systolic blood pressure < 90 mmHg), tachycardia (heart rate > 110/min), bradycardia (heart rate < 50/min)		Secondary outcome measure(s): blood loss, intraoperative haemodynamic stability, postoperative pain, recovery of bowel movement, and complication rates	Secondary outcome measure(s): blood loss, intraoperative haemodynamic stability, postoperative pain, recovery of bowel movement, complication rates
	Other outcome measure(s): -		Other outcome measure(s): -	Other outcome measure(s): -
Barczynski 2014	Source: NCT01959711	No	Primary outcome measure(s): duration of surgery	Primary outcome measure(s): duration of surgery
	Primary outcome measure(s): duration of surgery (time frame: intraoperatively)			
	Secondary outcome measure(s): postoperative recovery including postoperative pain, length of hospital stay, time to		Secondary outcome measure(s): intraoperative blood loss, conversion rate, postoperative pain, prevalence of	Secondary outcome measure(s): blood loss, conversion rate,

(Continued)

oral intake, time to ambulation; blood loss (all: participants were followed for the duration of hospital stay, an expected average of 7 days); postoperative complications (up to 5 years after surgery) including: pneumothorax or haemothorax, surgical emphysema, chest infection, visceral injury, peritonitis or abscess, wound infection, neuralgia, and surgical access site herniation

shoulder-tip pain, additional analgesia requests, nausea and vomiting, time to oral intake, time to ambulation, length of hospital stay, total cost of the operation, postoperative complications (including long-term surgical access site herniation and need for hernia repair), and in cases of active tumours, also biochemical and clinical cure rate during 5-year follow-up

postoperative recovery, morbidity, costs

Other outcome measure(s): -

Other outcome measure(s): -
Other outcome measure(s): -

Mohammadi-Falah 2013

N/T

Primary outcome measure(s): convalescence period, defined as the period needed for complete recovery from the physical aftereffects of surgery and return to normal personal jobs

Primary outcome measure(s): -

Secondary outcome measure(s): -
Secondary outcome measure(s): -

Other outcome measure(s): blood loss, operative time, open conversion, analgesic requirement dose, oral intake, ambulation, hospital stay, postoperative pain

Other outcome measure(s): -

Rubinstein 2005

N/T

Primary outcome measure(s): -
Primary outcome measure(s): -

Secondary outcome measure(s): -
Secondary outcome measure(s): -

Other outcome measure(s): operative time, estimated blood loss, specimen weight, number of open conversions, analgesic requirement, days to oral intake, days to ambulation, days of hospital stay, complications, median convalescence, number of deaths

Other outcome measure(s): operative time, estimated blood loss, specimen weight, number of open conversions, analgesic requirement, days to oral intake, days to ambulation, days of hospital stay; complications, median convalescence, number of deaths

Fernández-Cruz 1996

N/T

Primary outcome measure(s): -
Primary outcome measure(s): -

(Continued)

Secondary outcome measure(s): -	Secondary outcome measure(s): -
Other outcome measure(s): paCO ₂ , arterial pH, operating time, intraoperative bleeding, need for blood transfusion, analgesic dose requirements, hospital stay, time to achieve normal activity, complications	Other outcome measure(s): paCO ₂ , arterial pH, operating time, intraoperative bleeding, need for blood transfusion, analgesic dose requirements, hospital stay, time to achieve normal activity, complications

- denotes not reported

^aTrial document(s) refers to all available information from published design papers, and sources other than regular publications (e.g. FDA/EMA documents, manufacturer's websites, trial registers)

^bPublication(s) refers to trial information published in scientific journals (primary reference, duplicate publications, companion documents, or multiple reports of a primary trial)

^cOther outcome measures refer to all outcomes not specified as primary or secondary outcome measures

EMA: European Medicines Agency; **FDA:** Food and Drug Administration (US); **N/T:** no trial document available

Appendix 8. High risk of outcome reporting bias according to ORBIT classification

Trial ID	Outcome	High risk of bias (category A) ^a	High risk of bias (category D) ^b	High risk of bias (category E) ^c	High risk of bias (category G) ^d
Chai 2017	N/A				
Barczynski 2014	N/A				
Mommadi-Fallah 2013	N/A				
Rubinstein 2005	N/A				
Fernández-Cruz 1996	N/A				

^aClear that outcome was measured and analysed; trial report states that outcome was analysed, but only reports that result was not significant (Classification A, table 2, [Kirkham 2010](#))

^bClear that outcome was measured and analysed; trial report states that outcome was analysed, but no results reported (Classification D, table 2, [Kirkham 2010](#))

^cClear that outcome was measured, but not necessarily analysed; judgement says likely to have been analysed, but not reported because of non-significant results (Classification E, table 2, [Kirkham 2010](#))

^dUnclear whether the outcome was measured; not mentioned, but clinical judgement says likely to have been measured and analysed, but not reported on the basis of non-significant results (Classification G, table 2, [Kirkham 2010](#))

N/A: not applicable; **ORBIT:** Outcome Reporting Bias In Trials

Appendix 9. Definition of endpoint measurement

Trial ID	All-cause mortality	Morbidity	Health-related quality of life	Operative parameters	Postoperative parameters
Chai 2017	N/D	N/D	N/I	<p>"Operative time was calculated from the first incision to the final stitch"</p> <p>"Amount of blood loss was calculated by the volume of suction and the weight of the gauze"</p>	"Postoperative pain was evaluated using a VAS with a range from 0 (no pain) to 10 (worst pain). VAS was checked 3 to 5 times daily, and expressed as a daily mean value"
Barczynski 2014	N/R	"Surgical complications were classified according to the Dindo-Clavien classification"	N/I	"Duration of surgery was calculated from skin incision to skin closure. Intraoperative blood loss was calculated on the basis of hematocrit assessment in the saline fluid used for irrigation in relation to the blood hematocrit"	"Pain intensity was assessed using the visual analog scale (VAS) at 4, 8, 12, 24, and 48 hours post-operatively"
Mohammadi-Fallah 2013	Deaths	Late complications, such as portal-site hernia	N/I	N/R	"...the convalescence period, defined as the period needed for complete recovery from the physical aftereffects of surgery and return to normal personal jobs"
Rubinstein 2005	"Mortality due to various unrelated causes ... during the 6-year follow-up"	N/D	N/I	N/R	"Convalescence was defined as the period needed for complete recovery from the physical aftereffects of surgery"
Fernández-Cruz 1996	N/R	N/D	N/I	"The following parameters were evaluated in each patient with retroperitoneal and with transperitoneal approaches: operative time, estimated blood loss, length of hospital stay, postoperative analgesic requirements, and the time needed to achieve normal activity"	N/R

N/D: not defined; **N/I:** not investigated; **N/R:** not reported; **VAS:** visual analogue scale

Appendix 10. Definition of endpoint measurement

Trial ID	Severe/serious adverse events	Socioeconomic effects
Chai 2017	N/D	N/D
Barczynski 2014	N/D	N/D
Mohammadi-Fallah 2013	N/D	"...The convalescence period, defined as the period needed for complete recovery from the physical aftereffects of surgery and return to normal personal jobs"
Rubinstein 2005	N/D	"Convalescence was defined as the period needed for complete recovery from the physical aftereffects of surgery"
Fernández-Cruz 1996	N/D	The following parameters were evaluated in each participant with retroperitoneal and with transperitoneal approaches: operative time, estimated blood loss, length of hospital stay, postoperative analgesic requirements, and the time needed to achieve normal activity
N/D: not defined		

Appendix 11. Adverse events (I)

Trial ID	Intervention and comparator	Partici- pants in- cluded in analysis (N)	Deaths (N)	Deaths (%)	Partici- pants with at least one adverse event (N)	Partici- pants with at least one adverse event (%)	Partici- pants with at least one severe or serious ad- verse event (N)	Partici- pants with at least one severe or serious ad- verse event (%)
Chai 2017	I: posterior retroperitoneoscopic adrenalectomy	41	0	0	-	-	-	-
	C: transperitoneal adrenalectomy	42	0	0	-	-	1	2.4
Barczynski 2014	I: posterior retroperitoneoscopic adrenalectomy	33	-	-	6	18.2	-	-
	C: transperitoneal adrenalectomy	32	-	-	15	46.8	-	-
Moham- di-Fallah 2013	I: retroperitoneal adrenalectomy	12	0	0	1	8.3	0	0
	C: transperitoneal adrenalectomy	11	0	0	1	9.1	0	0
Rubinstein 2005	I: retroperitoneal adrenalectomy	32	4	12.5	1	3.1	-	-
	C: transperitoneal adrenalectomy	25	1	4	2	8	-	-
Fernán- dez-Cruz 1996	I: retroperitoneal adrenalectomy	8	-	-	0	0	-	-
	C: transperitoneal adrenalectomy	7	-	-	2	28.6	-	-
- denotes not reported								
C: comparator; I: intervention								

Appendix 12. Adverse events (II)

Trial ID	Intervention and comparator	Participants included in analysis (N)	Participants discontinuing trial due to an adverse event (N)	Participants discontinuing trial due to an adverse event (%)
Chai 2017	I: retroperitoneal adrenalectomy	41	-	-
	C: transperitoneal adrenalectomy	42	-	-
Barczynski 2014	I: retroperitoneal adrenalectomy	33	-	-
	C: transperitoneal adrenalectomy	32	-	-
Mohammadi-Falah 2013	I: retroperitoneal adrenalectomy	12	-	-
	C: transperitoneal adrenalectomy	11	-	-
Rubinstein 2005	I: retroperitoneal adrenalectomy	32	-	-
	C: transperitoneal adrenalectomy	25	-	-
Fernández-Cruz 1996	I: retroperitoneal adrenalectomy	8	-	-
	C: transperitoneal adrenalectomy	7	-	-

- denotes not reported

C: comparator; I: intervention

Appendix 13. Adverse events (III)

Trial ID	Intervention and comparator	Participants included in analysis (N)	Participants with a specific adverse event (description)	Participants with at least one specific adverse events (N)	Participants with at least one specific adverse event (%)
Chai 2017	I: retroperitoneal adrenalectomy	41	Surgical site herniation	0	0
	C: transperitoneal adrenalectomy	42	Surgical site herniation	0	0
Barczynski 2014	I: posterior retroperitoneoscopic adrenalectomy	33	(1) Massive subcutaneous emphysema (2) Surgical access site herniation	(1) 2 (2) 0	(1) 6.2 (2) 0
	C: transperitoneal adrenalectomy	32	(1) Massive subcutaneous emphysema	(1) 1 (2) 5	(1) 3.1 (2) 15.5

(Continued)

(2) Surgical access site herniation					
Mohammad-Fallah 2013	I: retroperitoneal adrenalectomy	12	-	-	
	C: transperitoneal adrenalectomy	11	-	-	
Rubinstein 2005	I: retroperitoneal adrenalectomy	32	Port site hernia	0	0
	C: transperitoneal adrenalectomy	25	Port site hernia	2	8
Fernández-Cruz 1996	I: retroperitoneal adrenalectomy	8	-	-	-
	C: transperitoneal adrenalectomy	7	-	-	-

- denotes not reported

C: comparator; I: intervention

Appendix 14. Survey of study investigators providing information on included trials

Trial ID	Date trial author was contacted	Date trial author replied	Date trial author was asked for additional information (short summary)	Date trial author provided data (short summary)
Chai 2017	Will be contacted for the next review update			
Barczynski 2014	26 May 2015 by email, and 17 September 2015 by regular mail	No reply	N/A	N/A
Mohammadi-Fallah 2013	No email address available, sent written message by regular mail on 26 May 2015 and 17 September 2015	No reply	N/A	N/A
Rubinstein 2005	26 May 2015 by email, and 17 September 2015 by regular mail	No reply	N/A	N/A
Fernández-Cruz 1996	26 May 2015 by email, and 17 September 2015 by regular mail	No reply	N/A	N/A

N/A: not applicable

Appendix 15. Checklist to aid consistency and reproducibility of GRADE assessments

(1) All-cause mortality	(2) Early morbidity	(3) Late morbidity	(4) Health-related quality of life	(5) Socio-economic effects
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(Continued)

						(time to return to normal activities, time to ambulation, length of hospital stay)
Trial limitations (risk of bias) ^a	Was random sequence generation used (i.e. no potential for selection bias)?	Yes	Yes	Yes	Not reported	Yes
	Was allocation concealment used (i.e. no potential for selection bias)?	Unclear	Unclear	Unclear		Unclear
	Was there blinding of participants and personnel (i.e. no potential for performance bias) or was outcome measurement not likely to be influenced by lack of blinding?	Yes	No (↓)	No (↓)		Unclear
	Was there blinding of outcome assessment (i.e. no potential for detection bias), or was outcome measurement not likely to be influenced by lack of blinding?	Yes	No (↓)	No (↓)		Unclear
	Was an objective outcome used?	Yes	Unclear	Unclear		Unclear
	Were more than 80% of participants enrolled in trials included in the analysis (i.e. no potential reporting bias)? ^e	Yes	Yes	Yes		Yes
	Were data reported consistently for the outcome of interest (i.e. no potential selective reporting)?	Yes	Unclear	Unclear		Yes
	No other biases reported (i.e. no potential of other bias)?	Yes	Yes	Yes		Yes
Inconsistency ^b	Did the trials end up as scheduled (i.e. not stopped early)?	Yes	Yes	Yes		Yes
	Point estimates did not vary widely?	N/A	Yes	Yes		Yes
	To what extent did confidence intervals overlap (substantial: all confidence intervals overlap at least one of the included studies point estimate; some: confidence intervals overlap but not all overlap at least one point estimate; no: at least one outlier: where the confidence interval of some of the studies do not overlap with those of most included studies)?	N/A	Substantial	Substantial		Substantial, Substantial. Some
	Was the direction of effect consistent?	N/A	Yes	Yes		Yes, Yes, No

(Continued)

	What was the magnitude of statistical heterogeneity (as measured by I^2) - low ($I^2 < 40\%$), moderate ($I^2 40\%$ to 60%), high $I^2 > 60\%$?	N/A	Moderate	Low	Moderate, Low, High (↓)
	Was the test for heterogeneity statistically significant ($P < 0.1$)?	N/A	Not statistically significant	Not statistically significant	Statistically significant (↓)
Indirectness ^a	Were the populations in included studies applicable to the decision context?	Highly applicable	Highly applicable	Highly applicable	Highly applicable
	Were the interventions in the included studies applicable to the decision context?	Highly applicable	Highly applicable	Highly applicable	Highly applicable
	Was the included outcome not a surrogate outcome?	Yes	Yes	Yes	Unclear
	Was the outcome timeframe sufficient?	Sufficient	Sufficient	Sufficient	Sufficient
	Were the conclusions based on direct comparisons?	Yes	Yes	Yes	Yes
Imprecision ^c	Was the confidence interval for the pooled estimate not consistent with benefit and harm?	N/A	No (↓)	Yes	No (↓), Yes, No (↓)
	What is the magnitude of the median sample size (high: 300 participants, intermediate: 100 to 300 participants, low: < 100 participants)? ^e	Low (↓)	Low (↓)	Low (↓)	Low (↓) to intermediate
	What was the magnitude of the number of included studies (large: > 10 studies, moderate: 5 to 10 studies, small: < 5 studies)? ^e	Small (↓)	Intermediate	Small (↓)	Small (↓), Small (↓), Moderate
	Was the outcome a common event (e.g. occurs more than 1/100)?	No	Yes	Yes	N/A
Publication bias ^d	Was a comprehensive search conducted?	Yes	Yes	Yes	Yes
	Was grey literature searched?	Yes	Yes	Yes	Yes
	Were no restrictions applied to trial selection on the basis of language?	Yes	Yes	Yes	Yes
	There was no industry influence on studies included in the review?	Unclear	Unclear	Unclear	Unclear
	There was no evidence of funnel plot asymmetry?	N/A	N/A	N/A	N/A
	There was no discrepancy in findings between published and unpublished trials?	N/A	N/A	N/A	N/A

^aQuestions on risk of bias are answered in relation to the majority of the aggregated evidence in the meta-analysis, rather than to individual trials

(Continued)

^bQuestions on inconsistency are primarily based on visual assessment of forest plots and the statistical quantification of heterogeneity is based on I^2

^cWhen judging the width of the confidence interval, it is recommended to use a clinical decision threshold to assess whether the imprecision is clinically meaningful

^dQuestions address comprehensiveness of the search strategy, industry influence, funnel plot asymmetry, and discrepancies between published and unpublished trials

^eDepends on the context of the systematic review area

(**⬇**): key item for potential downgrading the quality of the evidence (GRADE) as shown in the footnotes of the 'Summary of finding' table(s); **N/A**: not applicable

CONTRIBUTIONS OF AUTHORS

All review authors read and approved the final review draft.

Alberto Arezzo (AA): protocol drafting, search strategy development, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review of drafts and future review updates.

Alberto Bullano (AB): acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review of drafts and future review updates.

Giovanni G Cochetti (GGC): protocol drafting, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review of drafts and future review updates.

Roberto Cirocchi (RC): protocol drafting, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review of drafts and future review updates.

Justus J Randolph (JR): protocol drafting, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review of drafts and future review updates.

Ettore E Mearini (EM): protocol drafting, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review of drafts and future review updates.

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Hendrick Jaap Bonjer (HJB): data extraction, data analysis, data interpretation, review of drafts and future review updates.

Mario Morino (MM): data extraction, data analysis, data interpretation, review of drafts and future review updates.

DECLARATIONS OF INTEREST

Alberto Arezzo: none known.

Alberto Bullano: none known.

Giovanni G Cochetti: none known.

Roberto Cirocchi: none known.

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Hendrick Jaap Bonjer: none known.

Mario Morino: none known.

SOURCES OF SUPPORT

Internal sources

- none, Other.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

All-cause morbidity was not reported in the included trials. Therefore, we changed this outcome to early and late morbidity, and included specific adverse events (e.g. liver injury, splenic injury, vascular injury, pneumothorax or haemothorax, massive subcutaneous emphysema, surgical access site herniation) under these outcome measures, depending on when the outcome was measured (early morbidity 30 to 60 days post surgery, and late morbidity at latest available follow-up). Consequently, we changed our primary outcomes from 'all-cause mortality, all-cause morbidity, adverse events' to 'all-cause mortality, early morbidity, late morbidity'. We also adapted our 'Summary of finding' table from '1. All-cause mortality, 2. All-cause morbidity, 3. Adverse events, 4. Health-related quality of life, 5. Socioeconomic effects' to '1. All-cause mortality, 2. Early morbidity, 3. Late morbidity, 4. Health-related quality of life, 5. Socioeconomic effects'.

We redefined operative blood loss from the maximum decrease in haemoglobin, to quantities of blood loss in millilitres (mL) measured at the end of surgery, as the decrease in haemoglobin was not reported.

NOTES

We have based parts of the background and methods sections, the appendices, additional tables, and Figures 1 to 3 of this review on a standard template established by the Cochrane Metabolic and Endocrine Disorders Group.

INDEX TERMS

Medical Subject Headings (MeSH)

Activities of Daily Living; Adrenal Gland Neoplasms [*surgery]; Adrenalectomy [adverse effects] [*methods] [mortality]; Cause of Death; Laparoscopy [adverse effects] [*methods]; Length of Stay; Peritoneum; Randomized Controlled Trials as Topic; Retroperitoneal Space

MeSH check words

Adult; Female; Humans; Male